610.5
J65b

SEP 28 1914

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice.

Vol. XXV.—No. 284.] BALTIMORE, OCTOBER, 1914. [Price, 25 Cents

CONTENTS.

	PAGE
Experimental Observations on the Suprarenal Glands with Especial Reference to the Functions of their Interrenal Portions. (Illustrated.) By S. J. Crowe and Geo. B. Wislocki	287
A Clinical Study of Primary Carcinoma of the Fallopian Tube. (Illustrated.) By Cecil W. Vest, M. D.	305
The Normal Differential Leucocyte Count. By Sydney R. Miller, M. D.	317
The Quarter Centennial Anniversary of the Opening of The Johns Hopkins Hospital and the Twenty-first Anniversary of the Opening of The Medical School	322
The Herter Lectures for 1914	322

EXPERIMENTAL OBSERVATIONS ON THE SUPRARENAL GLANDS WITH ESPECIAL REFERENCE TO THE FUNCTIONS OF THEIR INTERRENAL PORTIONS.

By S. J. Crowe and Geo. B. Wislocki, Baltimore.

(From the Hunterian Laboratory for Experimental Surgery.)

Notwithstanding the numerous investigations which have been undertaken since the time of Thomas Addison and Brown-Sequard, but little is known regarding the physiology of the normal suprarenal bodies, or the symptomatology resulting from lesions of these glands. Experimental and clinical studies, however, have shown that the suprarenals are necessary to life; that they are of importance in the regulation of carbohydrate metabolism; and that the secretion of the medullary cells contains a non-proteid substance (adrenalin) which produces, when injected even in minute quantities, a marked rise in blood pressure and a contraction of most of the muscular structures which receive their nerve supply through the sympathetic. It has also been shown that the action of adrenalin on these organs is, in many respects, similar to the effect produced by an electrical stimulation of the sympathetic nerves supplying them.

Such facts as the pigmentation of Basedow's disease; the hypertrophy of the medulla of the adrenals after removal of the thymus; the hypertrophy of the lymph glands and thymus in association with tuberculosis of both the suprarenal glands, together with some of the results of experimental studies on the metabolism of the sugars, all suggest an inter-relation between the suprarenals, thymus, thyroid, lymphatic system and pancreas. In several instances autopsy has disclosed an adenoma of the cortical cells of the suprarenal capsules in children in whom the most striking clinical symptoms were a precocious development of the sexual organs, an overgrowth of hair on the body and an abnormal deposit of fat. Further evidence of a relationship between the adrenals and the sexual apparatus is afforded by the enlargement of these glands during pregnancy. The increase in size of the adrenals during pregnancy is due to the hypertrophy of the cells of the cortical layer; the chromaffin cells are but little changed.[1] Furthermore, the cells of the corpus luteum are morphologically and histologically similar to those of the zona fasciculata of the adrenal, and it has been suggested that the corpus luteum of pregnancy is really a "temporary cortical suprarenal."[2] It has also been stated that the complete extirpation of both adrenals in a pregnant animal is not fatal; if the corpus luteum cells, however, are removed at the same time, the animal will not survive.

A suprarenal gland, like the hypophysis cerebri, is composed of two main divisions, which are histologically and embryologically distinct. A *total extirpation* of both the suprarenal bodies is, in most animals, speedily followed by symptoms of muscular prostration, tremors, subnormal temperature, and within a few days by death. On account of the widespread distribution of the *chromaffin system*,[3] it is impossible to study

[1] This statement is made by Biedl, but disputed by Wiesel and others.

[2] Rolleston: The Goulstonian Lectures on the Suprarenal Bodies. Brit. Med. Jour., 1895, Vol. I, p. 629.

[3] The paraganglia along the abdominal sympathetic chains and the organs of Zuckerkandl all contain cells histologically identical with those in the medulla of the adrenal, and their extracts have been found to contain a blood-pressure raising principle similar to adrenalin.

the effects of a total removal of this type of tissue alone. There is conclusive evidence, however, that animals deprived of the *entire cortical portion* of both adrenals will not survive, even though the medullary portion remains intact. This was strikingly shown by Biedl [4] in 1899, while working at the Zoological Station in Naples. In some species of fish the cortex and medulla of the suprarenal glands are separate bodies; a median or interrenal body is made up of cortical tissue alone, while the medullary portion is represented by a series of quite separate bodies which lie in close relationship to the ganglia of the sympathetic chain. In such fishes the extirpation of the interrenal body, leaving the medullary tissue intact, results quite regularly in death within three weeks, the only symptom being a progressive muscular weakness. If a small portion of the cortical tissue is left, however, the fish will recover; and at the end of four weeks this remaining fragment shows a marked hypertrophy, both grossly and microscopically.

Experiments on mammals have shown that an animal may survive the removal of both suprarenal glands for an indefinite period, provided accessory tissue is present. In many instances, this accessory tissue consists of cortical cells alone; it undergoes hypertrophic changes following the removal of both suprarenal glands; and the animal promptly succumbs when this accessory gland is removed.

In general, then, the medullary portion of the adrenal may be compared with the posterior lobe of the hypophysis, and the cortical part of the adrenal with the anterior lobe of the hypophysis. Acromegaly is apparently due to an over-activity of the anterior lobe and is associated with an increase of the eosinophilic cells; while general systemic disturbances of growth and the delayed acquirement of secondary sexual characteristics are referable to an insufficiency of this portion of the gland. On the other hand, definite changes in carbohydrate metabolism result from experimentally produced insufficiency of the posterior lobe, while injection of posterior lobe extracts greatly accelerates metabolic processes—leading to a lowering of carbohydrate tolerance (often to the point of spontaneous glycosuria) and, if long continued, to marked emaciation.

Addison's disease, with the asthenia, pigmentation of the skin, low blood pressure and gastro-intestinal disturbances, is ascribed to the destruction of a large portion of the chromaffin system (Wiesel), usually due to tuberculosis. As was previously mentioned, an hypertrophy of the sexual organs, adiposity, and an overgrowth of hair on the body have been the striking symptoms in children with an adenoma of the cortical portion of the adrenals, but aside from this and a similar suprarenal virilism or hirsutism met with in adults,[5] the writer knows of no syndrome which has been ascribed to either an over or under activity of this part of the gland. On account of the great size of the cortex of the adrenal in the fœtus,[6] the histological structure of this portion of the gland, its hypertrophy during pregnancy, and the experimental demonstration that it is the cortex of the adrenal which is necessary to life, all make it seem possible that careful experimental studies may show that this portion of the adrenal is as important a member of the ductless gland series as is the anterior lobe of the hypophysis.

Furthermore, there seems to be a quite definite relation between the suprarenal bodies, the thymus and the lymphatic system. Although this relationship is not emphasized in any of the text-books or special articles we have seen dealing with the physiology and pathology of the adrenals, there are as many as fifty clinical cases to be found in the literature of the past ten years with titles such as: "An Unusual Case of Addison's Disease with a Status Lymphaticus;" or, "A Case of Status Lymphaticus with a Complete Destruction of the Medulla of the Adrenals." It will be shown later that we have been able to produce a condition in animals which closely simulates a true status lymphaticus.

It was with these general points in mind that the following experiments were undertaken. Up to the present time we have made observations on 26 animals. It was our purpose to study the immediate and remote effects of (1) a total removal of both the suprarenal bodies in young and in old animals; (2) an adrenal insufficiency produced by the operative removal of portions of the gland at intervals of weeks or months. In the dog, a good exposure of the adrenals may be obtained either through a right or a left rectus incision, and the desired amount removed, or the adrenal (lumbar) vein ligated, without loss of blood or injury to the neighboring structures. We have made no attempt at the operation to separate the cortex from the medulla, and in the following observations the portion of the gland removed always includes both cortex and medulla.

The results of our experiences may be considered under the following headings:

I. The effects of a total removal of both suprarenal bodies.

II. The effects of removal of either the right or the left adrenal alone.

III. The relative importance of the cortex and medulla of the adrenal.

IV. The relation of the adrenal to carbohydrate metabolism.

V. Transplantation of the adrenals.

VI. The possible relation between the suprarenal bodies, the thymus and the lymphatic system.

I. The Effects of a Total Removal of Both Suprarenal Bodies.

We have removed both suprarenal glands either at one operation or by successive stages in nine animals, and are able to fully confirm the observations of Biedl and others, that in the dog the suprarenal bodies are necessary to life. Abelous and Langlois [7] have found that in frogs, guinea-pigs and rabbits a

[4] Biedl: Innere Sekretion, 1913, I. Teil, p. 376.

[5] Wiesel, J.: Krankheiten der Nebennieren. Lewandowsky's Handbuch der Neurologie, Band IV, Pt. III, 375.

[6] Refer to article by Elliott and Armour: The Development of the Cortex in the Human Suprarenal Gland and its Condition in Hemicephaly. Jour. Path. and Bact., 1911, Vol. XV, p. 481.

[7] Abelous and Langlois: Note sur les fonctions des capsules surrénals chez la grenouille. Compte rend. de la Soc. Biol., 1891, Vol. XLIII, pp. 792-800. La mort des grenouilles aprés la destruction des deux capsules surrénals. Compte rend. de la Soc. Biol., 1891, XLIII, pp. 855-859.

total extirpation of these glands is always fatal; in case of survival, a careful search will invariably reveal hypertrophied accessory adrenal tissue.[8]

On account of the size of the animal and the comparatively infrequent occurrence of accessory tissue, all of our experiments have been made on the dog. We have tried to determine:

(A) The influence of age and sex on the length of life after a total removal of both adrenals.

(B) The length of life after:
  (a) Total removal of both adrenals at one operation.
  (b) Gradual ablation of both adrenals by successive operations.

(C) The circulatory disturbances resulting from a total removal of both adrenals at one operation.

(D) The general manifestations of adrenal insufficiency.

(A) We have been unable to show that the age and sex of the animal has any influence on the results of the operation. Although one of the younger animals (Observation 5), a female, aged 6 months, succumbed on the eighth day; and another (Observation 15), a male, aged 6 months, survived four days, the average length of life in the remaining eight observations was less than twenty-four hours. In general, the younger animals succumb more promptly than do the older ones; frequently they will not survive a partial extirpation of the adrenals, although as much as one-fourth of one gland is left. This was rather surprising to us, since our observations on experimental hyphophysectomy in the canine[9] show that the age has a definite influence on the length of life after a total removal of the hypophysis. Of thirteen total hypophysectomies on adult animals, the average period before death was two days; while the average length of life of the eight puppies in which the same operative procedure was carried out was 11 days.

It has been stated that a total extirpation of both adrenals is not fatal in a pregnant animal, the function of the cortex of the adrenal being taken up by the cells of the corpus luteum. We have, as yet, made no studies on pregnant animals, but some very suggestive experiments along this line were made in 1912-13 by Harvey and Stewart.[10]

We may conclude, therefore, in agreement with many other investigators, that the suprarenal glands are of vital importance. If they are removed the animal invariably succumbs, regardless of the age or sex, provided there is no accessory adrenal tissue to take up their function.

(B) It apparently makes but little difference in the length of life of the animal whether both adrenals are removed at one operation, or whether there is a gradual depletion by successive operations at intervals of weeks or months. In other words, it seems that there is no other tissue, with the exception of accessory bodies, that is capable of taking up the function of the adrenals, or at least not to a degree sufficient to prevent a fatal outcome when the last remaining fragment of the suprarenal gland is removed.

Table I will demonstrate this point.

(C) I am indebted to Dr. Wm. H. Howell for the following notes concerning the circulatory disturbances after a total removal of both adrenals. The animals were given an anæsthetic, artificial respiration instituted and a continuous kymographic record made of the blood-pressure, pulse-rate and respiration for seven or eight hours following the removal of the suprarenal bodies. His conclusions are as follows:

(1) The immediate effect of the operation was a fall of mean blood-pressure (about 30 to 40 mm.) and a great increase in heart-rate. This latter effect is frequently seen after any abdominal operation, and is possibly not specific.

(2) For about three hours after the operation, the blood-pressure remains steady after a preliminary rise of 15 to 20 mm., while the pulse-rate steadily grows more rapid.

(3) After the fourth or fifth hour, the pressure rather abruptly begins to fall while the pulse-rate continues to grow more rapid.

Both the main facts noted, namely, the steady increase in heart-rate,[11] beginning practically at once after the operation, and the final somewhat suddenly appearing but gradually increasing fall in blood-pressure, would seem to meet a rational explanation on the view of a gradual disappearance of epinephrin from the circulation.

(D) The general symptoms which appear after a total removal of both adrenals are in many respects similar to those produced by a total hypophysectomy. As a rule, the animal promptly recovers from the anæsthetic and for several hours is in an apparently normal condition. He then begins to show a loss of appetite; symptoms of muscular weakness; and, what is most striking, a gradually increasing drowsiness. These animals act as if they had been given a large dose of morphia. There is a lowering of the body temperature, as low as 25° C.

[8] These accessory bodies may be miniature adrenals composed of epithelial and chromaffin tissue; or they may be made up of epithelial (cortical) cells alone. They are rarely present in dogs and guinea-pigs, but are very commonly found in rabbits and rats, making these latter animals unfit for experimental studies.

The following are the various situations in which accessory adrenal bodies may be found:

1. In the vicinity of the adrenals, lying in connective tissue as an independent body.
2. Under the capsule or in the substance of the kidneys.
3. Between the vena cava and aorta, or in the walls of the blood-vessels (suprarenal artery and vein, vena cava, renal vein).
4. In the sympathetic ganglia.
5. Between the transverse colon and spleen, in the ligamentum mesocolon transversum.
6. Under the capsule or in the right lobe of the liver.
7. In the pancreas.
8. In the retroperitoneal tissue; in the region of the sacro-iliac synchondrosis; along the entire vas deferens; between the testicle and the epididymis; in the broad ligaments; along the Fallopian tubes and in the ovaries.

[9] Crowe, Cushing and Homans: Experimental Hypophysectomy. The Johns Hopkins Bulletin, 1910, Vol. XXI, pp. 127-169.

[10] Not published.

[11] It was called to my attention by Dr. L. F. Barker that in some clinical cases of tachycardia the heart-rate seems to be slowed after the administration of adrenalin solution by mouth several times a day for a period of two or three weeks.

in some cases, and an accompanying muscular rigidity with tremors. The rigidity and tremors will disappear temporarily if the animal is wrapped in warm blankets and the body temperature raised by this means to the normal level.

In several of our animals there has been a series of general convulsive seizures preceding death. This symptom seems to be independent of the lowering of the body temperature, and in no instance has the post-mortem examination revealed any gross lesion in the central nervous system. Convulsive seizures have also been observed in animals with an "almost total" removal of both adrenals. In one animal there were frequent convulsive attacks for a week following the last of a series of operations; although only one-tenth of one adrenal was left in situ in this case, the animal finally recovered and was apparently normal for the succeeding eight months of observation (cf. Fig. 9, dog II). These findings suggest that some cases of clinically idiopathic epilepsy may be due to a disturbance of function, either of the cortex of the adrenals or of the chromaffin system.

The following protocol, together with a kymographic record of the carotid pressure, will serve to illustrate the symptoms and general condition of an animal with adrenal insufficiency.

TABLE I.

TOTAL REMOVAL OF BOTH ADRENALS.

	Weight.	Operations.	Duration of Life.	Remarks.
Obs. 2. Male, age 6 mos.	*Oct. 30, 1912.* 11¾ lbs.	*Oct. 30, 1912.* 9/10 of rt. adrenal removed.	Interval of 7 days between 1st and 2d op'n.	*Apr. 28, 1913.* Convulsions beginning 18 hours after removal of all but a fragment of adrenal tissue, and recurring at intervals for a week.
	Mar. 5, 1913. 19 lbs.	*Nov. 6, 1912.* Left adrenal removed.	Interval of 172 days between 2d and 3d op'n.	
	Apr. 1, 1913. 21 lbs.	*Apr. 27, 1913.* Portion of remaining hypertrophied fragment of rt. adrenal removed.	Interval of 187 days between 3d and 4th op'n.	
	Apr. 30, 1913. 20 lbs.			
	Oct. 8, 1913. 27¼ lbs.	*Nov. 10, 1913.* Removal of remaining rt. adrenal.	Interval of 18 hours between 4th op'n and death.	
	Nov. 10, 1913. 29¾ lbs.			
Obs. 3. Male, age 1 yr.	*Mar. 30, 1913.* 28½ lbs.	*Nov. 13, 1912.* 9/10 of rt. adrenal removed.	Interval of 7 days between 1st and 2d op'n.	Although there was a viable transplant of six months' standing, it proved to be of no functional value.
		Nov. 20, 1912. Entire lft. adrenal removed.	Interval of 175 days between 2d and 3d op'n.	
		May 1½, 1914. Fragment of rt. adrenal removed.	Interval of 24 hours between 3d Op'n and death.	
Obs. 5. Female, age 6 mos.	.....	*Feb. 5, 1913.* Both adrenals removed.	Death after 8 days.	*Feb. 10, 1913.* 60 cc. urine for 24 hours. Dull and listless.
				Feb. 11, 1913. Pulse 125. Temp. 36.1°. Refuses food.
				Feb. 12, 1913. Pulse 115. Temp. 31.6°. Very weak and unsteady on feet. 85 cc. urine voided during past 24 hours.
Obs. 6. Female, age 2 yrs.	*Feb. 10, 1913.* 7 lbs.	*Feb. 10, 1913.* Both adrenals removed.	Death after 24 hours.	
Obs. 13. Male, age 6 mos.	*Apr. 13, 1913.* 19¾ lbs.	*Apr. 13, 1913.* Left adrenal removed.	Interval of 35 days between 1st and 2d op'n.	
		May 18, 1913. Rt. adrenal removed.	Interval of 12 hours between 2d op'n and death.	
Obs. 14. Female, age 6 mos.	*Apr. 20, 1913.* 12¼ lbs.	*Apr. 20, 1913.* Left adrenal removed.	Interval of 7 days between 1st and 2d op'n.	
	Apr. 30, 1913. 12 lbs.	*Apr. 27, 1913.* ⅔ rt. adrenal removed.	Interval of 7 days between 2d and 3d op'n.	
		May 4, 1913. Remainder of rt. adrenal removed.	Interval of 24 hours between 3d op'n and death.	
Obs. 15. Male, age 6 mos.	*May 4, 1913.* 18½ lbs.	*May 4, 1913.* Left adrenal and 9/10 of rt. removed.	Interval of 21 days between 1st and 2d op'n.	After 2d operation. Listless; will not voluntarily take food; subnormal temperature.
		May 25, 1913. Remaining hypertrophied fragment of rt. adrenal removed.	Interval of 4 days between 2d op'n and death.	Carotid pressure 45 mm.; tendency to anuria.
Obs. 16. Female, age 3 mos.	.....	*May 12, 1913.* Both adrenals removed.	Death after 12 hours.	This animal was used by Dr. Howell for observations on coagulations of the blood after extirpation of adrenals.
Obs. 17. Male, age 3 mos.	.....	*May 12, 1913.* Rt. adrenal and ⅔ of left removed.	Interval of 18 days between 1st and 2d op'n.	
		May 30, 1913. Remaining fragment of left adrenal removed.	Interval of 12 hours between 2d op'n and death.	

OBSERVATION 30.—A male fox terrier; age 1 year; weight 16 pounds.

Feb. 22, 1914 (11 a. m.).—An uncomplicated operation through an incision in the right rectus muscle. Removal of the entire right adrenal and all but a minute fragment (purposely left at the upper pole) of the left adrenal. A fragment of the right adrenal,

measuring 6 x 4 x 5 mm., was transplanted between the posterior sheath of the rectus and the transversalis muscle.

A catheterized specimen of urine before operation contained no reducing body, while the urine removed 30 minutes after the operation promptly reduced both Fehling's and Nylander's solutions.

Feb. 23, (2 p. m.).—Very dull; can be roused, but will not take food or milk. If placed on his feet, will slowly and unsteadily walk around the room for a few minutes, but soon lies down and falls asleep. The tongue and mucous membranes are dry, cold and pale. The pupils are contracted, but react normally to light. There is an extreme degree of general muscular rigidity with tremor, and an exaggeration of all the tendon reflexes. The pulse is feeble and irregular. The heart-beat, counted with the aid of a stethoscope, is 96 to the minute. The rectal temperature is 29° C.; respiration 18. There is no vomiting, no diarrhea nor convulsive seizures. By wrapping the animal in warm blankets, the body temperature was raised within one hour to 33.7° C.

This animal seemed entirely insensible to pain; the common carotid artery was exposed and the accompanying kymographic record made without the slightest evidence of discomfort. We have frequently seen animals in this "anæsthetic state" following a total removal of the hypophysis cerebri.

Repeated injections of a 1-1000 solution of commercial adrenalin produced the characteristic cardio-vascular response, but without any evidence of improvement in the general manifestations.

Feb. 24, (10 a. m.).—Comatose: femoral pulse barely palpable. No urine secreted for the past 24 hours. Respiration shallow and irregular; ceased about 11 a. m.

Autopsy.—Made immediately after death. Hemorrhage under the skin and in several of the organs, probably due to the intravenous administrations of adrenalin. What is of especial interest is a beginning disintegration of the remaining fragment of the left adrenal; it is quite apparent that we had cut off its blood supply at the time of the operation. The transplant under the rectus muscle is also going to pieces; certainly, it has been of no functional value.

II. The Effects of the Removal of Either the Right or the Left Adrenal Alone.

A transient glycosuria occurs quite regularly after any operative manipulation of either the right or the left suprarenal gland. We have examined catheterized specimens of urine in 18 animals, both before and at frequent intervals after the operation. In a large percentage of these animals the glycosuria appears within a few minutes after the operation on the adrenal, and persists from four to twenty-four hours. In some cases the urine contains as much as 40 grams to the liter of a substance which must be glucose, since it reduces Fehling's and Nylander's solution; ferments; forms crystals with phenylhydrazine acetate; and is dextrorotatory. In no instance did the glycosuria persist for more than twenty-four hours, and subsequent estimations of the tolerance for levulose and galactose failed to show any permanent disturbance of carbohydrate metabolism. This whole question will be more fully discussed in a subsequent section of this paper.

Aside from the appearance of a transient glycosuria, our experiences are in accord with those of others, namely: (1) No acute manifestations of adrenal insufficiency follow the removal of either the right or the left adrenal alone; (2) the remaining gland undergoes marked hypertrophic changes, and within a week or ten days after the operation may be almost double the original size. Some observers have noted an hypertrophy of the medulla as well as of the cortex. In our series, however, the compensating changes are confined to the cortical layer (Figs. 1 and 2, dog XI, plate I; and Fig. 4).

The thyroid, the hypophysis and the liver have shown no constant changes which may be ascribed to an adrenal insufficiency. We have not studied microscopically the changes in the glycogen content, although there is probably an increased glycogenolysis immediately following any operation on the adrenals. We have also been unable to see any striking changes in the pancreas, although the islets have not yet been studied with Bensley's stain.

The interstitial cells in the testes are not increased in number or in size, and the ovaries look normal.

III. The Relative Importance of the Cortex and the Medulla of the Adrenal.

The following group of experiments was made in order to determine which portion of the adrenal is of vital importance. The solution of this question is not so simple as was the differentiation of function of the two principal lobes of the hypophysis. It is a comparatively easy procedure to remove either the anterior or the posterior lobe of the hypophysis without interfering with the normal blood supply of the remaining part; this is impossible, however, in the adrenals, due to the anatomical relationship of the medulla to the cortex, and the peculiar arrangement of the blood supply.

It was first pointed out by Stilling,[12] who made some extirpation experiments on rabbits, that when one adrenal is removed the remaining gland undergoes a marked compensatory hypertrophy. He also made the important observation that it is the cortical portion which shows the hypertrophic changes. The extirpation experiments of Biedl upon fish mentioned above seem to demonstrate quite definitely that it is the interrenal or cortical portion of the gland which is of vital importance in this species of animals. Moreover, it has been pointed out by numerous observers, but disputed by others (Neusser and Wiesel[13]), that it is the cortical portion of the adrenals which hypertrophies during pregnancy. Rolleston has stated that the corpus luteum cells in the ovary of pregnant animals are "temporary cortical suprarenal glands," and in case the adrenals are extirpated during pregnancy, the function of the cortex is taken up by these lutean cells, at least to a degree sufficient to prevent the usual fatal outcome.

Our own observations seem to bear out the main contention of Biedl that it is the cortex which is the essential portion of the suprarenal glands. Our reasons for arriving at this conclusion are as follows:

(1) In the embryo the adrenals are relatively huge bodies and are composed mainly of cortical (epithelial) cells. At a later period, cells of the chromaffin system push their way into the center of this mass of cortical tissue, and, when the gland is fully developed, these cells constitute the medulla. Chro-

[12] Stilling; Note sur l' hypertrophie compénsatrice des capsules surrénals. Rev. de Med., 1885, VIII, pp. 459-461.

[13] Neusser and Wiesel. Die Erkrankungen der Nebennieren. Wien, 1910.

maffin tissue, similar in origin and structure to that composing the medulla of the adrenals, may be found on both sides of the abdominal aorta, in the sympathetic ganglia, in the walls of the blood-vessels, and forming definite bodies, such as Zuckerkandl's organs. This extraneous tissue has the same relation to the sympathetic nervous system as has the medulla of the adrenals, and its extracts (Zukerkandl's organs, for example,) contain a blood-pressure raising principle identical with adrenalin. Aside from its anatomical relation to the cortex, the medulla of the adrenal does not essentially differ from these other chromaffin bodies. In some animals, indeed, this intimate relationship is not present, the cortex being an entirely distinct and separate gland—the interrenal body. In such animals, death promptly ensues after a total extirpation of the interrenal body. If a fragment of this body is left intact, however, it undergoes hypertrophic changes, and the animal does not succumb.

(2) When an adrenal insufficiency is produced by the extirpation of either the right or the left adrenal in the dog, there is, as a rule, a very striking hypertrophy of the remaining gland. The increase in size of the hypertrophied adrenal is due to a rapid multiplication of cells in the cortex, and chiefly in the fascicular zone of the cortex (Figs. 1 and 2, dog XI, plate I). There is little or no enlargement of the medullary portion of the adrenal, as is best demonstrated by comparing, in the gross, a transverse section of the gland removed at operation with the one removed at autopsy several weeks later. Another important change found in the cortex of an adrenal undergoing acute hypertrophy is the variation from the normal in the amount and distribution of the lipoids.[1] These bodies are normally present in all three zones of the cortex, but most abundant in the fascicular zone, particularly in its outer third (Fig. 1, dog XI, plate I). In the hypertrophic gland of two or three weeks standing (Fig. 2, dog XI), the lipoids are most abundant in the glomerular zone; practically absent in the reticular zone; and very scanty in the fascicular zone. This marked disappearance of the lipoids in an adrenal undergoing hypertrophic changes reminds one of the behavior of the colloid in a severe case of Basedow's disease. This analogy may be carried still further, since an hypertrophied adrenal of long standing (examined two or three months instead of two or three weeks after the operation at which the insufficiency was established) frequently has a great excess of lipoids, collected in large irregular clumps and globules. This may, in a rough way, be compared with a colloid goitre.

(3) A long-standing chronic infection in an animal with an adrenal insufficiency frequently results in the destruction of the parenchymatous cells and a secondary fibrosis throughout the cortex of the remaining fragment of the adrenal. The medulla is but little injured, the chief seat of the lesion being the fascicular zone. Fig. 2, dog VIII, illustrates such a condition. This animal had a low-grade chronic infection of the upper respiratory passages (distemper) which persisted for a month; the terminal event was an acute bronchial pneumonia. The acute infection in this case was the probable cause of the numerous areas of focal necrosis in the fascicular zone. (A section of the normal gland removed at operation is shown in Fig. 1, dog VIII.) We have seen no marked lesion of the medullary portion as a result of an acute or chronic infection. It is of interest to note in this connection that hemorrhages and focal areas of cell necrosis are frequently seen in the cortex of the suprarenals after the subcutaneous injection of diphtheria toxine. This is particularly true in guinea-pigs, and has often been noted in clinical cases dying of some acute general infection.

These findings suggest that some of the symptoms present in clinical cases with acute or chronic infections may be referable to an insufficiency of the cortex of the adrenals, and that a rational therapeutic measure in such cases would be the administration of an extract prepared from the *cortex* of the adrenals. Further observations will be necessary to determine whether or not this theory is tenable.

(4) The illustration (dog III, plate I,) shows a complete distintegration of the cells of the fascicular or mid-cortex zone with a striking hypertrophy of the glomerular portion and an approximately normal reticular zone and medulla. This result was accidentally produced by the ligation of some of the larger vessels supplying a small fragment of one adrenal. By repeated operations, all of the adrenal had been removed with the exception of this small fragment of the upper pole of the right gland. After six months, during which the animal was in apparently perfect health, the larger vessels supplying this remaining hypertrophied fragment were ligated. Symptoms of adrenal insufficiency appeared soon after the operation; for two days the animal had frequent convulsive seizures, a subnormal temperature and an almost total anuria. Recovery gradually ensued, however, and at a fourth operation the remaining fragment of adrenal was further reduced in size by removing a fragment of its outer (cortical) portion; death followed twenty-four hours later. At the autopsy the adrenal shows the condition described above, and with the exception of a marked lymphatic hyperplasia (to be discussed in a later section), the other organs were normal. It seems quite evident in this case that death resulted from the impaired circulation of the zone fasciculata of the cortex of the adrenal; that the tremendous hypertrophy of the glomerular zone is probably of a compensatory nature; and that the well-preserved medulla, as much as was present at any time during the preceding six months, was not sufficient to keep the animal alive after the destruction of the fascicular zone.

[1] The technique we have employed for the demonstration of lipoids in the adrenal is as follows:

The stains are prepared by dissolving 2 grams of Na OH in 100 cc. of 70 per cent alcohol; Scharlach R or Sudan III is then added to the point of saturation. Filter into tightly closed staining dishes immediately before using. Frozen sections of the material fixed in 10 per cent formalin are transferred to the stain for 5 or 6 minutes. The sections are differentiated in 70 per cent alcohol for 15 or 20 seconds and washed in water. They are then counterstained in Ehrlich's hæmatoxylin and mounted in glycerine. If the cover-slip is ringed with paraffin, sections prepared in this way may be kept for two or three years.

IV. The Relation of the Adrenals to Carbohydrate Metabolism.

There is already a tremendous literature on the general subject of carbohydrate metabolism disturbances and their relation to lesions of the various ductless glands. It is needless to recount here the various theories and experimental results, since these have been admirably presented in the recent publications of Biedl,[l.c.] Macleod,[15] Cammidge,[16] von Noorden,[17] Eppinger, Falta and Rüdinger,[18] and Goetsch, Cushing and Jacobson.[19]

Our object in discussing this question is to show:

(1) That a transient glycosuria follows any operative manipulation of either the right or the left adrenal.

(2) This glycosuria response is probably not a result of the direct mechanical stimulation of the sympathetic nerves in the neighborhood of the glands; nor is it due to an increased output of adrenalin from the medullary portion of the adrenal.

(3) There is little or no permanent disturbance of the carbohydrate metabolism in animals with an adrenal insufficiency.

Table II is intended to show that any operative procedure on either the right or left adrenal; massage of the adrenal; and ligation of the lumbar vein (into which the adrenal vein empties) is followed by the appearance of glucose in the urine.

Our conclusion that the glycosuria observed after operation on the adrenal is not due to a direct stimulation of the sympathetic nerves in the neighborhood of the gland is in accord with the observations of Macleod and others.

Macleod showed: (a) that stimulation of the splanchnic nerves will produce a hyperglycæmia, provided the adrenals and their blood supply are intact; (b) stimulation of the left splanchnic nerve after ligation of the left adrenal vein was followed by a hyperglycæmia in only one of three observations; (c) stimulation of the left splanchnic nerve after the removal of the left adrenal does not produce a hyperglycæmia; (d) after complete severance of the hepatic plexus of nerves, stimulation of the splanchnic nerve (with the adrenal intact) does not cause the usual degree of hyperglycæmia, whereas electrical stimulation of the peripheral end of the cut plexus is followed by an increased sugar content in the circulating blood.

It seems definitely proven, therefore, that the functional integrity of the efferent nerve fibres to the liver depends on the presence of the suprarenal glands. In our own experiences, any operative procedure on either the right or the left adrenal will cause a glycosuria so long as a minute fragment of the adrenal remains.[20] It is possible to remove, by successive operations, one entire adrenal and as much as seven-eighths of the other with little or no permanent disturbance as a result. The remaining fragment of adrenal often contains medullary tissue that is almost microscopical in size (Fig. 6, dog II), still, any subsequent operative procedure for the purpose of further reducing the size or completely removing this fragment will cause glycosuria. On the other hand, an extensive dissection of the tissue at the site of an adrenal previously removed is never, in our experience, followed by the appearance of sugar in the urine. It seems, then, that the presence of a fragment of the adrenal, however small it may be, is necessary in order to produce this reaction.

The liberation of glycogen in the liver is apparently controlled to a certain extent by a hormone from the suprarenal glands. The intravenous administration of large amounts of commercial adrenalin will cause a glycosuria, as will fright, severe muscular exertion, and other things shown to be associated with an increased outpouring of adrenalin into the circulation. It seems improbable, however, that the small amount of medulla present in the remaining fragment of adrenal in some of our animals could possibly liberate enough adrenalin to produce the glycosuria so constantly found when the fragment is massaged or partially extirpated. If it were otherwise, one would at least expect to find some microscopical evidence of an increased activity of these medulla cells.

(3) The ductless gland control of carbohydrate metabolism constitutes an extremely complicated mechanism, and, as yet, no very satisfactory explanation has been offered as to the origin of many of the experimental and clinical glycosurias. The chromaffin system, including the suprarenal glands on the one hand, and the pancreas on the other, are the two main antagonists; the former accelerating and the latter inhibiting glycogenolysis. The diabetes following extirpation of the pancreas is supposed to be due to the unopposed activity of the chromaffin system. It is impossible to remove the entire chromaffin system, but our experiments on dogs have shown that there is no permanent raising or lowering of the carbohydrate tolerance in animals with only one-sixth or one-eighth of one adrenal remaining. A good example of the influence of an adrenal insufficiency on the carbohydrate metabolism is shown in the tabulated observations on dog II, given below. About four months after the establishment of an adrenal insufficiency, the tolerance for levulose was between 50 and 60 grams; and about 10 grams for galactose. A month later the tolerance for levulose had dropped to less than 20 grams, and for galactose to less than 7 grams. A still greater degree of insufficiency was established by removing a portion of the remaining adrenal; this operation was followed by a transient glycosuria, and one month later the tolerance for levulose had not returned to the normal level. Two observations made about one year after the original operation showed that the tolerance for levulose was certainly *not above* the normal.

[15] Macleod: Diabetes: Its Pathological Physiology, 1913.

[16] Cammidge: Glycosuria and Allied Conditions, 1913.

[17] von Noorden: New Aspects of Diabetes, 1912.

[18] Eppinger, Falta and Rüdinger: Über die Wechselwirkungen der Drüsen mit inneren Sekretion. Ztchr. f. klin. Med., 1908, XXVI, 1909, XXVII, 380.

[19] Goetsch, Cushing and Jacobson: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri. Bull. J. H. H., 1911, XXII, 165-190.

[20] In observation 8 there was no glycosuria following a total extirpation of the right adrenal.

TABLE II.

OBSERVATIONS ON THE APPEARANCE OF A TRANSIENT GLYCOSURIA AFTER OPERATIONS ON THE ADRENAL.

(For the complete data on these animals, refer to Table IV at end of article).

	Operation.	Glycosuria.	Nylander's	Fehling's.	Fermentation Polariscopic Test.	Remarks.
Obs. 2. Male, age 1 yr.	*Apr. 27, 1913.* Entire left and 9/10 of rt. adrenal had been removed 6 mos. previously. Further reduction of remaining fragment of rt. adrenal.	Transient—appearing 15 minutes after removal of fragment of adrenal.	+ +	+ +		
Obs. 3. Male, age 1 yr.	*Apr. 20, 1913.* Removal of left kidney.	No glycosuria	− −	− −		
	Apr. 6, 1913. Ether anæsthesia * for ½ hour. No operation.	No glycosuria	− −	− −	.....	3 specimens examined; negative during anæsthesia and 1 and 2 hrs. after.
	May 9, 1913. Ligation of vessels supplying remaining 1/10 of rt. adrenal.	Transient—lasting 3 hrs.; first appearing immediately after op'n.	+ +	+ +	.....	3 specimens examined; positive.
	May 14, 1913. Minute fragment of rt. adrenal removed.	Transient—first appearing immediately after op'n.	+ +	.....	.....	1 specimen examined; positive.
Obs. 8. Male, age 2 yrs.	*Feb. 19, 1913.* Rt. adrenal removed.	No glycosuria	− −	.....	Fermentation − −	Total urine for 6 hours after operation examined; negative.
Obs. 9. Female, age 2 yrs. Pregnant.	*Feb. 24, 1913.* Left adrenal and ⅔ rt. adrenal removed.	Transient—lasting 24 hours.....	+ +			
	May 19, 1913. About ¾ of remaining rt. adrenal removed.	Transient	+ +	+ +		
Obs. 11. Female, age 1½ yrs.	*Mar. 31, 1913.* Left adrenal removed.	Transient—first appearing immediately after operation.	+ +	+ +		
Obs. 12. Female, age 6 mos.	*Apr. 6, 1913.* Left adrenal removed.	Transient—first appearing immediately after operation.	+ +	.....	.....	Specimen examined before operation was negative. 1 specimen examined after op. positive. Urine collected following 12 hrs. was negative.
Obs. 13. Male, age 6 mos.	*Apr. 13, 1913.* Left adrenal removed.	Transient—first appearing 1¼ hrs. after operation.	+ +	.....	Polariscopic 4% Dextrorotary.	2 spec. examined before op'n.; negative. 2 spec. exam. after op'n.; positive.
	May 18, 1913. Rt. adrenal removed.	Transient	+ +	+ +	.....	Specimen examined before operation reduces slightly. 2 spec. exam. after op'n. give prompt reduction.
Obs. 14. Female, age 6 mos.	*Apr. 20, 1913.* Left adrenal removed.	Transient—first appearing 1½ hrs. after op'n.	+ +	+ +		
	Apr. 27, 1913. ⅔ rt. adrenal removed.	Transient—first appearing 30 minutes after op'n.	+ +			
	May 4, 1913. Remainder of rt. adrenal removed.	Transient	+ +			
Obs. 15. Male, age 6 mos.	*May 4, 1913.* Left adrenal and 9/10 of rt. adrenal removed.	Transient	+ +	.....	Fermentation + +	
	May 25, 1913. Remaining fragment of rt. adrenal removed.	Transient	+ +	+ +		
Obs. 17. Male, age 3 mos.	*May 12, 1913.* Rt. adrenal and ⅔ of left removed.	Transient—lasting 18 hours.	+ +	+ +		
	May 30, 1913. Remainder of left adrenal removed.	Transient	.....	+ +	.....	Spec. examined before op'n; negative. 1 spec. exam. after op'n.; positive.
Obs. 18. Male, age 1½ yrs.	*May 25, 1913.* Ligation of rt. lumbar vein.	Transient	.....	+ +		
	June 8, 1913 Rt. adrenal removed.	Transient—first appearing immediately after op'n.	+ +	.....	.....	Spec. exam. before op'n.; negative. 1 spec. exam. after op'n.; positive.
Obs. 19. Male, age —.	*June 8, 1913.* Left adrenal massaged for 7 minutes.	Transient—appearing 20 min. after massage.	+ +			
Obs. 20. Male, age ½ yr.	*Nov. 23, 1913.* Rt. adrenal removed.	Transient—appearing ½ hr. after op'n.	+ +	+ +		
	Dec. 7, 1913. 9/10 of left adrenal removed. Adrenal vein ligated.	Transient—lasting 7 hrs.; appearing 20 min. after op'n.	+ +	.....	.....	1 spec. exam. before op'n.; negative. 2 spec. exam. after op'n.; positive.
	Feb. 22, 1914. Dissection in region where rt. adrenal was previously removed.	No glycosuria	− −			

* Ether anæsthesia was administered in all the operations of this series.

TABLE II.—Continued.

	Operation.	Glycosuria.	Nylander's	Fehling's.	Fermentation Polariscopic Test.	Remarks.
Obs. 22. Female, age 3 mos.	*Nov. 30, 1913.* Left adrenal removed. Rt. lumbar vein ligated.	Transient—lasting 20 hours.....	+ +	+ +		
	Dec. 14, 1913. 9/10 of rt. adrenal removed.	Transient—lasting 20 hours.....	+ +			
Obs. 23. Male, age 3 mos.	*Nov. 30, 1913.* Rt. adrenal removed. Left lumbar vein ligated.	Transient—lasting 24 hrs. after op'n.; first appearing 15 min. after op'n.	+ +			
	Dec. 14, 1913. 9/10 of left adrenal removed.	Transient—lasting 24 hours.....	+ +			
Obs. 25. Female, age 6 mos.	*Feb. 1, 1914.* Left adrenal and ¾ of rt. adrenal removed.	Transient—lasting 24 hours.....	+ +			
Obs. 26. Male, age 3 mos.	*Feb. 1, 1914.* Left adrenal and ¾ of rt. adrenal removed.	Transient—lasting 24 hours.....	+ +			
Obs. 30. Male, age 1 yr.	*Feb. 22, 1914.* Rt. adrenal and ¾ of left adrenal removed. Left lumbar vein ligated.	Transient—appearing ½ hour after op'n.	+ +			

TABLE III.

CARBOHYDRATE OBSERVATIONS ON DOGS WITH AN ADRENAL INSUFFICIENCY.

	Date.	Wgt.	Operation.	* Calculated tolerance (levulose, galactose).	Amt. given with stomach-tube.	Fehling's.	Nylander's.	Remarks.
Obs. 2. Male, age 6 mos.	Oct. 30, 1912	11¾ lbs.	Rem. 9/10 rt. adrenal.					
	Nov. 6, 1912	.....	Rem. lft. adrenal.					
	Feb. 25, 1913	.....	.....	26.5 gm.	50 gm. levulose	−	−	
	Mar. 1, 1913	.....	.....	" "	70 " "	+	+	
	Mar. 2, 1913	.....	.....	" "	60 " "	+	+	
	Mar. 3, 1913	.....	.....	5.1 "	30 " galactose	+	+	
	Mar. 4, 1913	19 lbs.	.....	" "	10 " "	−	+	
	Apr. 1, 1913	21 lbs.	.....	32.6 "				
	Apr. 5, 1913	.....	.....	" "	50 gm. levulose	+		
	Apr. 7, 1913	.....	.....	" "	40 " "	+	+	
	Apr. 8, 1913	.....	.....	" "	30 " "	+	+	
	Apr. 11, 1913	21 lbs.	.....	" "	20 " "	+	+	
	Apr. 12, 1913	.....	.....	6.5 "	7 " galactose	+	+	
	Apr. 27, 1913	.....	Removal of piece (10 x 12 mm.) of remaining fragment, rt. adr.	.....	.....	+	+	Transient glycosuria beginning ½ hr. after op'n.: convulsive seizures next A. M.
	Apr. 30, 1913	20 lbs.	.....					
	May 29, 1913	.....	.....	31 gm.	25 gm. levulose	+	+	
	Jun. 9, 1913	.....	.....	" "	31 " "	−	+	
	Oct. 8, 1913	27¼ lbs.	.....	42.4 "				
	Oct. 22, 1913	.....	.....	" "	43.5 gm. levulose	+	+	
	Oct. 23, 1913	.....	.....	" "	34.5 " "	+	+	
	Nov. 10, 1913	29¾ lbs.	Remaining hypertrophied fragment of rt. adrenal removed (cf. Figs. 5 and 6). Death 24 hrs. after.	.....	.....	.....	.....	Transient glycosuria.
Obs. 3. Male, age 1 yr.	Nov. 13, 1912	.....	Rem. 9/10 rt. adrenal.					
	Nov. 20, 1912	.....	Rem. entire left adrenal.					
	Mar. 1, 1913	.....	.....	49.8 gm.	60 gm. levulose	+	+	
	Mar. 3, 1913	.....	.....	" "	50 " "	−	−	
	Mar. 26, 1913	.....	.....	" "	70 " "	+	+	

TABLE III.—Continued.

	Date.	Wgt.	Operation.	* Calculated tolerance (levulose, galactose).	Amt. given with stomach-tube.	Fehling's.	Nylander's.	Remarks.
Obs. 3. Male, age 1 year.	Mar. 28, 1913	28½ lbs.	.....	49.8 gm.	60 gm. levulose	+	+	
	Apr. 1, 1913	.....	.....	8.7 "	10 " galactose	+	+	
	Apr. 2, 1913	.....	.....	" "	5 " "	−	−	
	Apr. 6, 1913	27½ lbs.	Ether anæsthesia for ½ hr.; no. op.	8.5 "	.....	−	−	
	Apr. 12, 1913	27 lbs.	.....	8.1 "	9 gm. galactose	+	+	
	Apr. 19, 1913	.....	.....	48.3 "	37 " levulose	−	+	
	May 9, 1913	.....	Ligation of vessels to remaining portion of rt. adrenal.	" "	.....	+	+	Transient glycosuria appearing 1 hr. after operation: convulsive seizures.
	May 14, 1913	.....	1/10 of remaining hypertrophied fragment on rt. removed. Death 24 hrs. later.	" "	.....	+	+	Transient glycosuria.
Obs. 9. Female, age 1½ yrs.	Feb. 24, 1913	12½ lbs.	Rem. lft. adrenal. Rem. ⅔ rt. adrenal.	.....	.....	+	+	Transient glycosuria for 24 hrs.
	Feb. 28, 1913	.....	.....	22.3 gm.	50 gm. levulose	+	+	
	Mar. 1, 1913	.....	.....	" "	40 " "	+	+	
	Mar. 2, 1913	.....	.....	" "	30 " "	+	+	
	Mar. 4, 1913	.....	.....	" "	10 " "	−	−	
	Apr. 1, 1913	.....	.....	" "	40 " "	+	+	
	Apr. 3, 1913	.....	.....	3.7 "	10 " galactose	−	−	
	Apr. 8, 1913	.....	.....	23.17 "	20 " levulose	−	−	
	Apr. 12, 1913	13 lbs.	.....	3.9 "	5 " galactose	+	+	
	May 19, 1913	.....	Removal of ¾ remaining hypertrophied fragment of rt. adrenal. Death 24 hrs. later.	.....	.....	+	+	Transient glycosuria on massaging adrenal before removal.

* Tolerance calculated after G. Quarta, Zeitschrift für Biol., V. 49, p. 522.

TOLERANZGRENZEN DER ZUCKERARTEN BEIM NORMALEN HUNDE PRO KG. KÖRPERGEWICHT.

Autoren.		Dextrose.	Lävulose.	Saccharose.	Laktose.	Galaktose.
F. Hoppe-Seyler: Virchows Archiv., 1856, Bd. 10 S. 144		−	−	20-30	−	−
Hofmeister: Archiv. f. exp. Path. u. Pharm., 1889, Bd. 25, S. 240		1, 9-2, 5 2, 9-5, 8	−	3, 6 nur Lävulose ausgeschieden.	0, 4-0, 8	−
W. Schlesinger: Wien. klin. Wchnschr., 1902, S. 30		10-11	−	−	−	−
R. Luzzatto: Archiv. f. exp. Path. u. Pharm., 1904, Bd. 25, S. 107		−	−	−	1, 1	0, 06
Boeri und De Andreis: Policlin. V. Med., 1898, S. 477		4-6 (nüchtern) 10-13 (b. Ehrnahr.)	−	−	−	−
G. Quarta Zeitschrift für Biol., V. 49, p. 522	Männliche Hunde	3, 20 5 3, 80 4, 25	2, 75 3, 05 3 3, 65	−	0, 80 2 1, 60 1, 75	− − − −
	Durchschnitt	4, 06	3, 11	−	1, 54	−
	Weibliche Hunde	10, 70 9, 15 11	3, 23 3, 50 4	−	2, 30 5, 90 3, 55	− − −
	Durchschnitt	10, 28	3, 58	−	3, 92	−

At autopsy, the remaining fragment of adrenal in this animal was found to contain a few medulla cells, but scarcely recognizable with the naked eye (Figs. 5 and 6, dog II). Microscopical examination showed that there was no hypertrophy nor other evidence of excessive activity of the medulla, a striking contrast in this respect to the cells of the three layers of the cortex.

It is apparent, then, that when the accelerating influence of the adrenals is removed, the inhibiting influence of the pancreas is counteracted by some of the other accelerators of glycogen mobilization.

V. Transplantation of the Adrenals.

In making transplants of the adrenals we have adhered to the principle emphasized by W. S. Halsted[21] that an existing "physiological deficit" is one of the essentials to a successful "take."

We undertook these transplantation experiments with the hope that we might be able to determine:

(1) Whether a fragment of cortex alone will "take" if transplanted into the kidney or the abdominal wall.

(2) Whether such a graft will suffice to keep the animal alive after a total extirpation of both adrenals.

In regard to the first point, the microscopical examination of the graft has disclosed approximately normal-looking viable cells of the cortex in several instances. The majority of such grafts, however, undergo degenerative changes and are eventually replaced with scar tissue. Even when large fragments containing both cortex and medulla, are transplanted, the cortical cells may survive (Figs. 7 and 8, dog III), but the chromaffin elements entirely disappear.

We have made no attempt to transplant the entire gland by merely loosening it from its bed and maintaining the original blood-supply, although von Haberer[22] has shown that grafts made in this way are often functional as well as microscopical "takes."

In order to prove the second point, it must be shown that the graft is of functional value. This test is made by removing the last remaining fragment of the original adrenal. Here again we have been unsuccessful, as is shown by Observation 3. In this animal (cf. table IV) about nine-tenths of the right adrenal was removed on Nov. 13, 1912, and a fragment of the portion removed was transplanted between the rectus and the peritoneum. One week later the entire left adrenal was extirpated. On May 9, 1913, about six months after the original operation, the larger vessels supplying the remaining fragment of the right adrenal were ligated; this operation was followed by convulsive seizures, subnormal temperature, loss of appetite and other symptoms of an acute adrenal insufficiency. The animal gradually recovered, however, and on May 14, 1913, about one-third of the remaining portion of the right adrenal was removed. Again the symptoms of an adrenal insufficiency appeared and death ensued twenty-four hours later. The microscopical appearance of the portion of the adrenal removed on May 14 is shown in Fig. 1, dog III, plate I. There is a necrosis of almost the entire fascicular zone, apparently due to an interference with the blood supply, produced by the ligation of the vessels on May 9; the glomerular zone is greatly hypertrophied, but the cells of the medulla are approximately normal in appearance. The engrafted fragment is embedded in scar tissue, but is well vascularized (Figs. 7 and 8, dog III). The normal architecture has become distorted by the ingrowth of fibrous tissue and only isolated groups of adrenal cells are seen. These cells, however, all contain lipoids and are of the cortical rather than the chromaffin type. The specific stains for chromaffin tissue fail to disclose any cells of this type, so we must conclude that the medullary portion of the graft has been absorbed. This is possibly due to the fact that a sufficient degree of "physiological deficit," as far as the chromaffin system is concerned, is not produced by the partial extirpation of the adrenals. If this is true, it precludes the idea that the negative functional value of such a graft, as the one described above, is due to the fact that it contains no viable medullary cells. The only explanation we can offer for the failure of the above experiment is that the engrafted fragment of adrenal was deprived of its normal nerve supply. We have repeatedly had animals to survive and develop normally with but a minute fragment of one adrenal (no larger than the engrafted portion in Observation 3) remaining in its original bed. Such a fragment becomes embedded in fibrous tissue and acquires a collateral circulation as does a graft; it still retains or regains its nerve connections, however, since massage or partial extirpation of the gland, or stimulation of the sympathetic nerves in the neighborhood, will produce a transient glycosuria, while none of these manipulations on a graft are followed by a glycosuric response, provided all the adrenal tissue has been removed from its normal situation. On the other hand, v. Haberer has found that when an adrenal is mobilized so as to retain its normal blood-supply and is buried in the adjoining upper pole of the kidney, about fifty per cent of the animals will survive a total extirpation of the remaining adrenal; in other words, the adrenal thus transplanted to the kidney continues to function.

VI. The Possible Relation Between the Suprarenal Bodies, the Thymus, and the Lymphatic System.

An interesting combination of status thymico-lymphaticus in association with changes in other organs is seen in Addison's disease. Even in the older literature on Addison's disease[23] a local or general hyperplasia of the lymphatic system is frequently noted in the autopsy reports. Most often it is the mesenteric and retroperitoneal glands and the lymph follicles in the walls of the intestines that are swollen, while those in the neck, axillæ and groins show but little change.

[21] Halsted, W. S.: The Transplantation of Parathyroid Glands in Dogs. Proceedings of the Soc. for Exper. Biol. and Med., 1908, v, 74-77.

[22] v. Haberer: Experimentelle Verlagerung der Nebenniere in die Niere. Archiv. f. klin. Chir., 1908, LXXXVI, 399.

[23] Averbeck. Die Addisonische Krankheit. Erlangen, 1869.

On the other hand, it was noted by Wiesel,[24] in 1904, that many of the individuals coming to autopsy with status thymicolymphaticus have a striking hypoplasia of the chromaffin system. These observations were confirmed by v. Neusser,[25] Bittorf,[26] and others. Hedinger[27] has studied a large number of cases with this point in mind and comes to the conclusion that status thymicus and status lymphaticus are entirely different conditions. In the former, the chromaffin system is usually normal in appearance and amount, but there are hypertrophic changes in the cortex of the adrenals; while in status lymphaticus degenerative or atrophic changes are frequently found in the medulla of the adrenal with but little or no change in the cortex.[28]

The only references we have seen to any experimental observations concerning the relation between the adrenals and the lymphatic system is the brief article published in 1899 by Auld,[29] and the reference made by Schaefer[30] in the Oliver-Sharpey lectures, in 1908, concerning the effects of extirpation of the spleen and adrenals in rats. Auld made a partial extirpation of the adrenal bodies in four dogs and states in his conclusions that in all four animals two phenomena were very apparent: (1) a great hypertrophy of the thymus; (2) a considerable enlargement of the spleen. There is no mention of changes in the lymph-glands, but he infers from his experiences that thymus feeding would possibly be of value in Addison's disease. Schaefer removed the spleen and adrenals in rats one month of age. Subsequent growth was normal; the animals were sacrificed four months later. There was no pigmentation, but a marked hyperplasia of the lymph glands.

Our attention was first directed to the possible relation between the adrenals and the lymphatic system by the autopsy findings in Observation 2. An adrenal insufficiency was established in this animal (cf. table IV) by removing at four different operations all but a minute fragment at the upper pole of one adrenal. For several days after the third operation the animal was in a semi-comatose condition and had frequent convulsive attacks; recovery gradually ensued, however, and during the succeeding eight months growth, development and sexual functions were apparently normal (Fig. 9, dog II). Death followed within a few hours after the removal of the remaining fragment of adrenal, demonstrating conclusively that this gland is necessary to life. The most striking feature at the autopsy was the large mesenteric, retroperitoneal, and mediastinal lymph glands, together with an atrophic thymus. Microscopical examination of the enlarged lymph glands show small, atrophic-looking lymph cords, but a very marked hyperplasia of the endothelial cells lining the lymph sinuses and of the large mononuclear cells in the germinal centers. These endothelial cells show but little evidence of phagocytosis and there is no increase in the number of leucocytes or eosinophilic elements. There was no evidence of a chronic infection; no skin eruption, and not an abnormal number of intestinal parasites.

The autopsy on Observation 3 also revealed a general enlargement of the lymph glands and, in addition, a persistent thymus. This was a full-grown adult, approximately one and a half years of age. Portions of the adrenal were removed at three different operations; and here again convulsive seizures, drowsiness—almost amounting to coma—and a scanty secretion of urine, all symptoms of an adrenal insufficiency, were present. At the third operation the large vessels supplying the remaining fragment of adrenal were ligated, leading to a necrosis of the fascicular zone of the cortex with no evident injury to the medulla (Fig. 1, dog III, plate I).

There was a general enlargement of the lymph glands, but the changes were most marked in those of the mesentery and retroperitoneal region. Microscopically, the germinal centers are prominent and filled with large mononuclears; the lymph cords are packed with small mononuclear cells; the endothelial cells lining the lymph sinuses are more abundant than in similar glands from control animals, but much less numerous than in Observation 2. The thymus is rich in small mononuclears, while the endothelial cells and Hassal's corpuscles are much less conspicuous than in control glands from animals of approximately the same age. The eosinophilic cells are more numerous than normal, and, for the most part, lying just outside the large blood vessels.

In Observation 20 the animal was about 18 months of age and the adrenal insufficiency was of four and a half months' duration. During this period there was a gain of five and a half pounds in weight, and the skeletal development and the sexual activities were apparently normal. The animal was accidentally killed. The autopsy revealed:

(1) A large vascular thymus, measuring 14 x 6 x 2.5 cm. It is packed with lymphocytes and has numerous large, well-preserved Hassal's bodies.

(2) Large mesenteric, retroperitoneal and mediastinal lymph glands.

(3) The inguinal and axillary glands show no marked increase in size, but are deeply pigmented. The pigment is contained in the endothelial cells lining the lymph sinuses.

(4) The lymph follicles in the lower portion of the small intestine are large and prominent, and microscopically, are seen to be composed almost entirely of large mononuclear or

---

[24] Wiesel. Zur Pathologie des chromaffinen Systemes. Virchows Archiv., 1904, CLXXVI, 103-114.

[25] Neusser u. Wiesel. Die Erkrankungen der Nebennieren. Wien, 1910.

[26] Bittorf: Die Pathologie der Nebennieren und des Morbus Addisonii. Jena, 1908.

[27] Hedinger: Keimzentrenbildung im Knochenmark des Oberschenkels bei Status Lymphaticus. Verhandl. d. med. Gesellsch. Basel. Sitzung, XXXI, Okt., 1907. Ueber Beziehungen Zwischen Status Lymphaticus und Morbus Addisonii. Verhandl. d. Deutsch. Path. Gesellsch. Dresden, 1907, p. 29.

[28] Wiesel: Pathologie des Thymus. Ergebnisse der Alg. Pathologie, 1911, XV, 416-728.

[29] Auld: Additional Observations on the Function of the Suprarenal Gland. Brit. Med. Jour., 1899, I, 1327.

[30] Schaefer: Oliver-Sharpey Lectures on the Present Condition of our Knowledge Regarding the Function of the Suprarenal Capsule. Brit. Med. Jour., 1908, I, 1277-1281 and 1346-1351.

TABLE IV.

NOTES ON THE MICROSCOPICAL APPEARANCE OF THE LYMPHATIC SYSTEM AND DUCTLESS GLANDS IN THE OBSERVATIONS MENTIONED IN THIS PAPER.

Case No.	Weight.	Operations.	Duration of life.	Post-mortem conditions.
Obs. 2. Male, age 6 mos.	*Oct. 30, 1912.* 11¾ lbs. *Mar. 5, 1913.* 19 lbs. *Apr. 1, 1913.* 21 lbs. *Apr. 11, 1913.* 21¼ lbs. *Apr. 30, 1913.* 20 lbs. *Oct. 8, 1913.* 27¼ lbs. *Nov. 10, 1913.* 29¾ lbs.	*Oct. 30, 1912.* Removal of 9/10 rt. adrenal. Fragment transplanted between peritoneum and rectus muscle. *Nov. 6, 1912.* Removal of entire left adrenal. Transplanted between peritoneum and rectus muscle. *Apr. 27, 1913.* Portion (10 x 12 m.m.) of the remaining rt. adrenal removed. *May 15, 1913.* Removal of area of transplants in abdominal wall; found to be replaced by scar tissue. *Nov. 10, 1913.* Removal remaining fragment of rt. adrenal.	One year and 10 days.... Death 18 hours after removal of last remaining fragment of right adrenal.	Animal well nourished. No remains of adrenal tissue; no accessory adrenals found. Most striking change is the *general enlargement of the lymph glands.* Testicles large. Other organs show no gross abnormality. *Microscopical.* (1) *Adrenal* (removed Oct. 30, 1912): Normal appearance and lipoid distribution. (2) *Adrenal* (removed Nov. 6, 1912): Beginning hypertrophy as shown by the increase in size and in lipoid content of the cells of the zona glomerulosa. No evident change in other zones of cortex nor in medulla. (3) *Adrenal* (removed Apr. 27, 1913): Marked hypertrophy of all zones of cortex; medulla small; cells show no evidence of hypertrophy. Lipoids most abundant in zona fasciculata; connected in large irregular globules in other two zones of cortex. (4) *Adrenal* (removed Nov. 10, 1913) (cf. Figs. 3 and 4): Large blood sinus in medulla; but very few medullary cells, and these show no hypertrophic changes. Hypertrophy chiefly in zona fasciculata. Lipoids abundant, but in large clumps—both intracellular and extracellular. *Thyroid:* Normal; cells cuboidal; no diminution in the amount of colloid. *Parathyroid:* Possibly shows hypertrophic changes (?). *Hypophysis:* Numerous colloidal bodies in posterior lobe and stalk; otherwise normal. *Testicle:* Abundant, normal-looking spermatozoa. No change in interstitial cells. *Pancreas:* Islets very vascular and unusually prominent—probably a definite hyperplasia. *Spleen:* Large Malpighian bodies due to hyperplasia of the endothelial (?) cells; but few lymphocytes. *Lymph Glands:* The lymph sinuses are packed with large endothelial cells containing pigment. The medullary cords are atrophic; but few lymphocytes surround the large germinal centers. *Thymus:* Was lost. *Transplant:* Replaced with scar tissue. No recognizable adrenal cells.
Obs. 3. Male, age 1 year.	*Nov. 13, 1912.* 22 lbs. *Mar. 30, 1913.* 28½ lbs. *Apr. 6, 1913.* 27½ lbs. *Apr. 11, 1913.* 27 lbs.	*Nov. 13, 1912.* Removal of 9/10 rt. adrenal. Fragment transplanted between peritoneum and rectus muscle. *Nov. 20, 1913.* Removal of entire left adrenal. No transplant. *May 9, 1913.* Ligation of larger vessels supplying remaining fragment of right adrenal. Had convulsive seizures for several days following this operation. *May 14, 1913.* Removal of minute fragment of rt. adrenal.	Six months ..... Death 24 hrs. later. Transplant of no functional value.	Animal well nourished. No accessory adrenals found. The transplant in abdominal wall is easily recognizable; can be seen shimmering through the peritoneum. Most striking is the *general enlargement of the lymph-glands.* The spleen is also enlarged. The thymus is large and vascular. Other organs show no gross changes. *Microscopical.* *Adrenal* (removed at autopsy, May 15): Necrosis of zona fasciculata; hypertrophy of the zona glomerulosa; approximately normal looking zona reticularis and medulla (cf. dog 3, plate I). *Pancreas:* Numerous prominent islets; vessels congested. *Spleen:* Hyperplasia of endothelial (?) cells in the germinal center of the Malpighian corpuscles; but few lymphocytes; many giant cells in pulp. *Hypophysis:* No increase in number of colloid bodies in posterior lobe, as in Obs. 2. *Liver:* Normal in appearance. *Thymus:* Vessels engorged with blood. *Hyperplasia of lymphocytes;* only small islands of medulla to be seen; Hassal's bodies are present, but not numerous. The thymus of this dog (1½ yrs. of age) looks much like that of a normal puppy. *Lymph glands:* Great *proliferation of the endothelial* (?) cells in the center of the germinal center, with an *increased number of lymphocytes;* the very picture of a status lymphaticus clinically. *Transplant* (cf. Figs. 5 and 6): Large clumps of lipoid containing cells (evidently cortex cells(embedded in fibrous tissue. Well vascularized. Specific chromaffin stains show that none of the medulla cells have survived. (There are numerous well-preserved cells of the cortex of the adrenal, but they proved to be of *no functional value.*

TABLE IV.—Continued.

Case No.	Weight.	Operations.	Duration of life.	Post-mortem conditions.
Obs. 4. Male, age 6 mos.	*Jan. 21, 1913.* 10-1/5 lbs.	*Jan. 24, 1913.* Removal entire right adrenal. No transplant. *Feb. 3. 1913.* Removal of 9/10 left adrenal, leaving part of upper pole. Transplant under peritoneum.	17 days ..... For a week preceding death (Feb. 10), had a subnormal temperature, tremors, drowsiness, etc.	Has rapidly lost weight since last operation. No cause found for death aside from adrenal insufficiency. *Microscopical.* (1) *Adrenal* (removed Jan. 24) : normal. (2) *Adrenal* (removed Feb. 3) : beginning hypertrophy as evidenced by an increase in size of the zona glomerulosa. In the middle and inner zone of the cortex the lipoids are more abundant than in control gland (Jan. 24). Cells of the medulla changed in appearance. *Pancreas:* Islets prominent and vessels engorged with blood. *Hypophysis:* Possibly an increase in eosinophilic cells in the anterior lobe; no change in posterior lobe. *Spleen:* No striking change. *Thyroid:* Normal. *Testicle:* Large numbers of interstitial cells, perhaps normal for an animal of this age. No spermatozoa seen. *Thymus:* Vessels engorged with blood. Composed chiefly of lymphocytes. But few Hassal's bodies to be seen; only small islands of medulla. This gland is probably undergoing acute hyperplastic changes; the histological appearance is similar to that of a normal puppy 10 days of age. *Transplant:* Round cell infiltration. Adrenal cells scarcely recognizable; numerous cholesterin crystals.
Obs. 5. Female, age 6 mos.	.....	*Feb. 5, 1913.* Removal of both adrenals. No transplant.	8 days ..... First symptoms of adrenal insufficiency appeared 5 days after operation (drowsiness, loss of appetite, subnormal temperature, muscular weakness).	No evident cause for death aside from adrenal insufficiency. No accessory adrenal tissue was found after a careful search. *Microscopical.* *Hypophysis:* A marked *diminution in the number of eosinophilic cells* in the anterior lobe; posterior lobe looks normal. *Ovary:* Looks normal. *Thymus:* Vessels engorged with blood. Hassal's bodies numerous and undergoing degenerative changes. Great predominence of lymphocytes. Approximately normal for an animal of this age. *Pancreas:* *Thyroid:* *Liver:* } Normal
Obs. 6. Female, age 2 years.	*Feb. 10, 1913.* 7 lbs.	*Feb. 10, 1913.* Removal of both adrenals. Transplant under peritoneum.	24 hours	No evident cause for death aside from the absence of both adrenals; no accessory adrenals found. *Microscopical.* *Thymus:* Vessels engorged with blood; large areas of hemorrhage. Otherwise only regressive changes are seen, probably due to the age of the animal.
Obs. 8. Male, age 2 yrs.	*Feb. 19, 1913.* 14½ lbs.	*Feb. 19, 1913.* Removal of entire rt. adrenal. Transplant under peritoneum.	One month. Animal had "distemper" for several weeks and a terminal acute bronchial pneumonia. Convulsive seizures for several days preceding death.	Chronic infection of upper respiratory passages and a bronchial pneumonia. (1) *Adrenal* removed at operation Feb. 19, measures 3 x .6 x .5 cm. (2) *Adrenal* removed at autopsy Nov. 19, measures 3.5 x .9 x .7 cm. *Liver:* shows cloudy swelling and focal necrosis. *Microscopical.* (1) *Adrenal* (removed Feb. 19) : normal. (2) *Adrenal* (removed May 19) (cf. dog 8, plate I) : Hypertrophy due to a multiplication of cells in the zona fasciculata; there is a very striking *interstitial fibrosis* in this zone, and *areas of focal necrosis.* The lipoids have almost entirely disappeared from the two inner zones of the cortex, but abnormally abundant in the glomerular zone. *Liver:* Areas of focal necrosis. *Thyroid:* Many of the alveoli filled with large desquamated epithelial cells; the colloid is scanty in amount and vacuolated. *Testicle:* Looks normal. *Spleen:* Hyperplasia Malpighian bodies. *Transplant:* Cortical cells still recognizable; cholesterin crystals.

TABLE IV.—Continued.

Case No.	Weight.	Operations.	Duration of life.	Post-mortem conditions.
Obs. 9. Pregnant female, age 2 years. Two normal puppies born March 31.	*Feb. 24, 1913.* 12½ lbs. *Apr. 11, 1913.* 13 lbs.	*Feb. 24, 1913.* Removal of entire left adrenal and ⅔ of right. Transplant under peritoneum. *May 19, 1913.* Removal of ⅔ remaining fragment of right adrenal. Transplant into upper pole of kidney.	Two months and 25 days. Death 24 hours after last operation.	Well nourished. No cause for death found other than adrenal insufficiency. Ovaries show large areas of luteum cells. *Microscopical.* *Adrenal:* Most striking is the absence of *hypertrophic change* in the portion of right adrenal removed at operation on May 19. There is also no variation from the normal in the amount and distribution of lipoids. *Ovary* (examined 7 wks. after birth of puppies): The greater part of both ovaries is composed of luteum cells. *Pancreas:* Islets large; vessels engorged with blood. *Lymph glands:* } No tissue removed at autopsy. *Thymus:* }
Obs. 11. Female, age 1½ years.	*Mar. 31, 1913.* 36 lbs. *Apr. 11, 1913.* 32 lbs.	*Mar. 31, 1913.* Removal of entire left adrenal. Transplant under peritoneum.	14 days	Death due to pneumonia. Most striking is the large *persistent thymus* and a *general enlargement of the lymph glands.* The right adrenal is almost twice the normal size. *Microscopical.* (1) *Adrenal* (removed at operation) (cf. dog II, plate I): Normal control. (2) *Adrenal* (autopsy) (cf. dog II, plate I): Hypertrophy of zona fasciculata; the other zones of cortex are also enlarged. The cells of the medulla are swollen; their nuclei larger and contain chromatin masses. The lipoids have all practically disappeared from the recticularis zone; are scanty in the fasciularis, but abundant in the glomerulosa. *Thyroid:* Many alveoli filled with desquamated epithelium; colloid vacuolated. *Hypophysis:* Great excess of the hyaline bodies of Herring in posterior lobe; the eosinophilic cells of the anterior lobe are small and inconspicuous, the predominating cells non-granular with a large vesicular nucleus (due to previous pregnancy ?). *Parathyroid:* Vessels engorged. *Ovary:* Normal. *Transplant:* Round cell infiltration; fatty degeneration. *Liver:* Focal necrosis around portal spaces. *Thymus:* Animal had a general infection.
Obs. 12. Female, age 6 mos.	*Apr. 6, 1913.* 20½ lbs. *Apr. 11, 1913.* 20 lbs.	*Apr. 6, 1913.* Removal of entire left adrenal.	One month and 19 days. Sacrificed on account of distemper.	Has rapidly lost weight during the past 2 weeks, due to a chronic infection of the upper air-passages. The rt. adrenal is hypertrophied. *Microscopical.* (1) *Adrenal* (removed at operation): Normal control. (2) *Adrenal* (autopsy): Hypertrophy due to multiplication of cells in the zona fasciculata; to a less extent in the other 2 zones of the cortex. Medulla is hyperæmic and vessels engorged with blood. Lipoids more abundant than normal in the zona glomerulosa; scanty in other cortical zones. *No focal necroses* nor fibrosis in cortex as in Obs. 8. *Thymus:* } Animal had a long standing chronic infection; *Lymph Glands:* } lymph glands are pigmented.
Obs. 13. Male, age 6 mos.	*Apr. 13, 1913.* 9¾ lbs.	*Apr. 13, 1913.* Removal of entire left adrenal. *May 18, 1913.* Removal of entire rt. adrenal.	One month and 5 days. Death 24 hours after last operation.	No cause for death found aside from adrenal insufficiency. Large thymus and hyperplasia of the mesenteric lymph glands; those in neck and groin not enlarged. *Microscopical.* (1) *Adrenal* (removed Apr. 13): Normal control. (2) *Adrenal* (removed May 18): *No hypertrophy* and no change in amount and distribution of lipoids. No change seen in the medulla. (Cause.) *Thymus:* The large endothelial cells are especially conspicuous; these cells show no evidence of phagocytosis. But few Hassal's bodies to be seen. No increase in the number of lymphocytes in the cortex. The size of the gland is apparently due largely to an hyperplasia of the endothelial cells in the medulla. *Lymph Glands:* Large germinal centers; but few lymphocytes. Hyperplasia of endothelial cells lining lymph sinuses. *Thyroid:* Normal.

TABLE IV.—Continued.

Case No.	Weight.	Operations.	Duration of life.	Post-mortem conditions.
Obs. 14. Female, age 6 mos.	*Apr. 20, 1913.* 12¼ lbs. *Apr. 30, 1913.* 12 lbs.	*Apr. 20, 1913.* Removal of entire left adrenal. No transplant. *Apr. 27, 1913.* Removal of ⅔ rt. adrenal. *May 4, 1913.* Removal of remainder of rt. adrenal.	14 days ..... Death 24 hours after 3d operation.	About 30 cc. of hemorrhagic fluid in the left pleural cavity, and early stage of bronchial pneumonia in lower lobe of left lung. No evidence of infection in the peritoneal cavity. No adrenal tissue left; no accessory adrenal bodies found. Mesenteric lymph glands seem larger than normal. *Microscopical.* *Thymus:* Very striking hyperæmia. The most marked change is the predominance of the cortex; there is but little medulla. Hassal's bodies degenerated. Many large mononuclear cells in the interlobular tissue and around the blood-vessels. (There is no control for this observation.) *Spleen:* Large amount of pigment in giant cells and endothelial cells of pulp; the Malpighian corpuscles are possibly larger than normal. *Thyroid:* Looks normal. *Adrenal* (removed May 4): No striking hypertrophy; lipoids are abundant in all three zones of cortex, and collected in large clumps.
Obs. 15. Male, age 6 mos.	*May 4, 1913.* 18½ lbs.	*May 4, 1913.* Partial removal of rt. adrenal, leaving about ⅓ at lower pole. Removal of entire left adrenal. Transplant fragment in kidney. *May 25, 1913.* Remaining fragment of rt. adrenal removed. Had doubled in size by actual measurement.	25 days ..... Animal succumbed on 4th day after operation.	No accessory adrenal tissue found. No evidence of infection. Has strikingly large thymus. Animal has rapidly lost weight since last operation. *Microscopical.* (1) *Adrenal* (removed May 4): Normal control. (2) *Adrenal* (removed May 25): Contains both cortex and medulla. Cortex greatly hypertrophied, largely due to increase in size of zona fasciculata. Medulla shows no hyperplasia either grossly or microscopically. There is an extensive fibrosis and round cell infiltration of the cortex; no such changes in the medulla. *Thyroid:* *Liver:* *Spleen:* *Testis:* } Show no marked change. *Thymus:* Lost. *Transplant* (Kidney): Adrenal cells viable around periphery; necrosis, round cell infiltration and cholesterin crystals in the central portion: of no functional value.
Obs. 17. Male, age —.	No record.	*May 12, 1913.* Removed entire rt. and ⅔ left adrenal. Transplant in kidney. *May 30, 1913.* Removal of remainder of left adrenal.	18 days ..... Death 18 hours after last operation.	No infection. No accessory adrenal tissue found. All of the adrenal had been removed on both sides. *Microscopical.* (1) *Adrenal* (removed May 12): Normal control. (2) *Adrenal* (removed May 30): hypertrophy not so great as in Obs. 15. Increase in size of zona fasciculata; no change seen in the medulla. Lipoids are more abundant than normal in zona glomerulosa; scanty in the other 2 zones of cortex in contrast to Obs. 15. *Transplant:* Scarcely recognizable; cholesterin crystals in central portion; a few viable cells around periphery: of no functional value.
Obs. 20. Male, age 1½ yrs.	*Nov. 20, 1913.* 18½ lbs. *Dec. 7, 1913.* 18½ lbs. *Feb. 22, 1914.* 24 lbs.	*Nov. 23, 1913.* Removal of entire rt. adrenal. Transplant in kidney. *Dec. 7, 1913.* Removal 9/10 lft. adrenal, leaving fragment at upper pole. Ligation of adrenal vein on left. Transplant in kidney. *Mar. 1, 1914.* Accidentally killed.	3 months and 7 days.....	Well nourished. Mesenteric and retroperitoneal *lymph glands much enlarged* those in neck, axillæ and groin are much enlarged and *deeply pigmented.* Remaining fragment of left adrenal much hypertrophied. No accessory adrenal found. Spleen not markedly enlarged, but the Malpighian bodies are very prominent. Pancreas, liver, heart and aorta look normal. Thyroid not enlarged. Stomach shows no evidence of ulcer. Intestines: Payer's patches from 2 to 3 cm. in diameter and very prominent. A few pin-worms in small intestine, but otherwise normal. Bone-marrow looks normal. The epiphyses of the long bones and ribs look normal. There is an extremely *large thymus,* measuring 14 x 6 x 2.5 cm.; the lower lobe extends down to the level of the apex of the heart. The tonsils are much enlarged, almost meeting in mid-line. *Microscopical.* *Thymus:* Hyperplasia of the lymphocytes (or small mononuclear elements). Only small areas of medulla. Hassal's bodies are numerous, large and well preserved. No increase in eosinophilic cells. *Lymph Gland* (mesentery): Large germinal centers filled with large mononuclear cells; no marked hyperplasia of the lymphocytes. Increase in size and number of endothelial cells lining lymph sinuses, many of which are loaded with pigment. Other lymph glands show endothelial hyperplasia and pigmentation. *Spleen:* Hyperplasia of large mononuclear cells in Malpighian bodies. Giant cells filled with pigment and many large endothelial cells in pulp. (1) *Adrenal* (removed Nov. 23): Normal control. (2) *Adrenal* (removed Dec. 7): Shows some evidence of *hyper-activity and hyperplasia of the cells of the medulla.* Hypertrophy of zona fasciculata of cortex. Lipoids scanty, but in all 3 zones of the cortex particularly abundant in the zona glomerulosa. (3) *Adrenal* (removed at autopsy): Cells of *medulla normal* in size and appearance, in contrast to specimen of Dec. 7. Very marked hypertrophy in zona fasciculata. Lipoids have almost entirely disappeared from inner 2 layers of cortex, but very abundant in outer zone. *Thyroid:* Vesicles filled with colloid; cells normal. *Liver:* Looks normal (but not stained for glycogen). *Tonsil:* Composed almost entirely of large mononuclear cells. *Testis:* Numerous spermatozoa; no change in size and number of interstitial cells. *Solitary Follicles* in intestine composed almost entirely of large mononuclear cells like those in germinal centers of lymph glands. But very few lymphocytes to be seen. *Pancreas:* Islets large and vessels engorged with blood.

TABLE IV.—Continued.

Case No.	Weight.	Operations.	Duration of life.	Post-mortem conditions.
Obs. 22. Female, age 3 mos.	*Nov. 30, 1913.* 7¼ lbs.	*Nov. 30, 1913.* Removal of entire left adrenal. Ligation rt. adrenal vein. Transplant in kidney. *Dec. 14, 1913.* Removal of rt. adrenal, leaving approximately 1/10 at upper pole.	15 days ..... Death 24 hours after last operation.	No infection of the respiratory tract or peritoneal cavity. Animal well nourished. Lymph glands not strikingly enlarged. Lungs, heart, liver, kidneys and intestines all look normal. Thymus atrophic. No ulcers in stomach. *Microscopical.* (1) *Adrenal* (removed Mar. 30): Normal control. (2) *Adrenal* (removed Dec. 14): Medulla cells look normal. Fibrosis and round cell infiltration in mid-zone of the cortex. Hypertrophy of cells of zona glomerulosa (much the same appearance as in dog 3). Lipoids abundant in outer zone; scanty in other zones of cortex. (3) *Adrenal* (removed at autopsy): Undergoing disintegration; apparently entire blood-supply has been cut off. *Thymus:* Undergoing regressive changes; but few lymphocytes. Hassal's bodies not numerous and degenerating. *Lymph Glands:* Large germinal centers; hyperplasia endothelial cells lining lymph sinuses. *Transplant:* Complete degeneration of medulla cells; mid-zone of cortex contains approximately normal-looking cells. *Thyroid:* Normal. *Ovary:* Normal.
Obs. 23. Male, age 3 mos.	*Nov. 30, 1913.* 7 lbs.	*Nov. 30, 1913.* Removal of entire right adrenal. Ligation of left adrenal vein. Transplant in kidney. *Dec. 14, 1913.* Removal of left adrenal, leaving approximately 1/10 at upper pole.	24 days ..... The animal survived 10 days with but a small fragment of cortex; no medulla found at autopsy. Had marked symptoms of adrenal insufficiency for 8 days preceding death.	Death apparently due to some infection of the gastro-intestinal tract; m. m. of stomach and entire small intestine is inflamed. œdematous and covered with mucus; no gastric ulcers. General enlargement of lymph glands. Thymus about normal for animal of this age—a striking contrast to Obs. 22. *Microscopical.* *Adrenals:* Approximately the same changes as described in Obs. 22—with the exception that the *remaining fragment at autopsy contained no medulla cells.* *Thymus:* many lymphocytes (in general is about normal for this age). *Lymph Gland:* Marked hyperplasia of germinal centers and endothelial cells lining lymph sinuses. No increase in leucocytes nor other evidence of general infection. *Transplant:* Complete degeneration. *Liver:* Normal. *Hypophysis:* Normal; no increase in hyaline bodies in posterior lobe.
Obs. 24. Female, age 3 mos.	*Dec. 8, 1913.* 9¾ lbs. *Dec. 16, 1913.* 9 lbs.	*Dec. 8, 1913.* Removal of entire right adrenal and all but 1/20 of left adrenal. Ligation of left adrenal vein.	10 days	There is a markd gastro-enteritis; the m. m. of stomach, small intestine, and colon is swollen and injected; no ulcerations seen. The m. m. of the œsophagus is not involved. *Microscopical.* *Adrenal* (removed at autopsy): Hypertrophy of the fascicular zone; almost complete disappearance of lipoids in all the zones of the cortex. Remaining medulla microscopical in size; medulla cells show no evidence of hypertrophy. *Lymph Glands* (animal had gastro-enteritis): Hyperplasia of endothelial cells lining lymph sinuses; lymphocytes not changed; no abnormal number of leucocytes. *Spleen:* Hemorrhages in pulp, also areas of focal necrosis; very marked proliferation of endothelial cells. Some Malpighian bodies contain no lymphocytes, only large endothelial cells.
Obs. 25. Female, age 6 mos.	*Feb. 1, 1914.* No record.	*Feb. 1, 1914.* Removal of entire left adrenal and ¾ of right. (The right adrenal was cut longitudinally.)	5 days	Since operation has gradually become more listless each day; temperature subnormal; appetite poor; marked muscular weakness. *Microscopical.* *Adrenal* (removed at autopsy): Undergoing degenerative change; apparently much of the blood supply was cut off at operation. *Lymph Glands* (mesenteric): Lymph sinuses filled with large endothelial cells; they show active phagocytosis of blood pigment. No hyperplasia of the germinal centers. *Other Organs* are approximately normal.
Obs. 26. Male, age 3 mos.	No record.	*Feb. 1, 1914.* Removal of entire left adrenal and ¾ of right. (The right adrenal was cut transversely, leaving the upper pole.) Adrenal vein on right not ligated.	24 hours	No cause for death found aside from an adrenal insufficiency. *Microscopical.* *Adrenal* (removed at autopsy): Has a good blood-supply; cells of cortex and medulla are well preserved.
Obs. 29. Male, age 1 year.	*Feb. 22, 1914.* 13½ lbs.	*Feb. 22, 1914.* Removal of entire right adrenal, and ⅔ of left. Mesenteric lymph gland removed for control. Transplant in abdominal wall.	17 days	Sacrificed on Mar. 10. The remaining portion of adrenal is hypertrophied. Abscess prostate; otherwise, organs look normal. *Microscopical.* *Adrenal* (removed at autopsy): Hypertrophy, chiefly the fascicular zone. Lipoids most abundant in reticular zone, the opposite to that seen in physiological hypertrophy uncomplicated by infection. *Lymph Glands:* Contain many leucocytes; otherwise no marked change from normal.
Obs. 30. Male, age 1 year.	*Feb. 23, 1914.* 16 lbs.	*Feb. 22, 1914.* Removal entire left adrenal and ¾ of rt.	48 hours	Hemorrhage into medulla of remaining fragment of adrenal. Refer to protocol in text. *Microscopical.* *Thymus:* Marked congestion and edema of entire gland; otherwise normal. *Adrenal* (removed at autopsy): Aside from hemorrhage, the gland is approximately normal in appearance. No change in lipoids.
Obs. 31. Male, age 4 mos.	No record.	*Feb. 23, 1914.* Removal entire left adrenal and ¾ of rt.	24 hours	No cause for death found aside from adrenal insufficiency. *Microscopical.* *Adrenal* (removed at autopsy): Beginning disintegration of the cells of both cortex and medulla, apparently due to insufficient blood-supply.

endothelial cells, similar to those in the germinal centers of the lymph glands.

(5) The spleen is slightly larger than normal and the Malpighian bodies stand out with great distinctness. The pulp contains numerous giant cells and endothelial cells filled with pigment. The center of the Malpighian bodies is filled with cells similar to those in the germinal centers of the lymph glands and in the solitary follicles of the small intestine. The lymphocytes are also more abundant than normal.

(6) The tonsils are much larger than in control animals of approximately the same age, and are made up of endothelial-like reticular cells with fragmented nuclei, but contain very few lymphocytes..

(7) The remainder of the ductless glands show no gross abnormality.

The increase in size of the lymph glands is apparently due to an hyperplasia of the cells lining the medullary sinuses and in the germinal centers. There is certainly no increase in number of the lymphocytes.

Similar observations were made on several other animals with a long-standing adrenal insufficiency. In order to make sure, however, that these changes in the lymph glands are really brought about by the partial extirpation of the adrenals, we have prepared a series of animals which are to be kept under observation for at least a year. In each of these animals as much of the adrenal was removed as is compatible with life. At the time of the operation, a mesenteric lymph gland was also extirpated as a control. Frequent observations will be made on the general blood picture and the changes in the lymphatic system. The results we hope to present in a subsequent communication.

Conclusions.

(1) In the dog, the suprarenal glands are vital organs, and it is probably the cortex rather than the medullary portion which is essential to life.

(2) After a partial extirpation of the adrenal, the remaining portion undergoes hypertrophic changes. The increase in size is due to a multiplication and enlargement of the cells of the cortex, chiefly in the fascicular zone; the medulla shows no hypertrophic changes, either grossly or microscopically.

(3) A chronic infection in an anmial with an adrenal insufficiency is occasionally associated with an interstitial fibrosis and destruction of the cells of the fascicular zone of the cortex. An acute general infection in an animal with an adrenal insufficiency produces in some instances focal areas of complete cell destruction (without hemorrhage) in the fascicular zone of the cortex of the remaining portion of the adrenal. In no instance have we seen hemorrhages or injury to the cells of the medulla of the adrenal resulting from an acute or chronic infection in the dog.

(4) After an "almost total" removal of both adrenals, the animals often have general convulsive seizures, a subnormal temperature and other symptoms of an acute adrenal insufficiency; in some instances, recovery gradually ensues after such symptoms and the animal subsequently develops in a normal manner as regards growth and sexual functions. There is also no change in disposition They increase in weight, but not to an abnormal extent. There is no polyuria.

(5) There is no permanent raising or lowering of the carbohydrate tolerance resulting from an adrenal insufficiency.

(6) A transient glycosuria follows the operative manipulation of either the right or the left adrenal.

(7) An autoplastic transplantation of a fragment of adrenal may "take," but is of no functional value. When a fragment of adrenal containing both cortex and medulla is transplanted, the cortical cells may survive, but the medullary cells are absorbed.

(8) There seeme to be a definite relationship between the suprarenal glands and the lymphatic system. The most striking feature at autopsy on an anmial with a long-standing adrenal insufficiency is the enlargement of the mesenteric and retroperitoneal lymph glands and the solitary lymph follicles in the walls of the intestine. Not infrequently there is also an hyperplasia of the thymus.

Further observations are being made to confirm these findings.

We wish to acknowledge the assistance of Drs. Whipple, Winternitz, Stevenson, and Park in the interpretation of the microscopical sections, and of Drs. Slack and Waldron for aid in the operative procedures.

DESCRIPTION OF PLATE I.

Dog XI.

Fig. 1.—Normal left adrenal removed at operation on March 31, 1913, from a female bull-dog weighing 36 lbs. Stained with Soudan III and H.

Fig. 2.—Showing hypertrophy of right adrenal which was removed at autopsy on April 14, 1913. Hypertrophy chiefly in zona fascicularis, although there is a marked increase in the size of the cells throughout the entire gland. Partial withdrawal of lipoids.

Dog VIII.

Fig. 1.—Normal right adrenal removed at operation on Feb. 19, 1913, from a male black-and-tan dog weighing 14½ lbs.

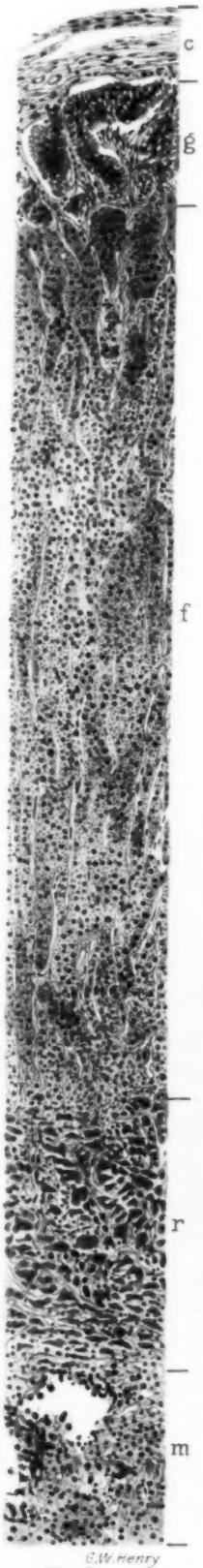
Fig. 2.—Left adrenal removed at autopsy one month later. Had chronic "distemper" which possibly accounts for the interstitial fibrosis in the zona fascicularis. Terminal pneumonia; numerous areas of focal necrosis in the zona fascicularis. No striking changes in the medulla.

Dog III.

Fig. 1.—Showing a complete disintegration of the cells of the zona fascicularis produced by ligating the larger vessels supplying an hypertrophied fragment of the right adrenal. (The entire left and 9/10 of the right had been removed at operation six months previously.) Ligation of the vessels was followed by convulsions and other symptoms of an acute adrenal insufficiency. This specimen was removed at autopsy five days after the ligation. Note the compensatory hypertrophy of the zona glomerulosa; the approximately normal looking medulla and zona reticularis.

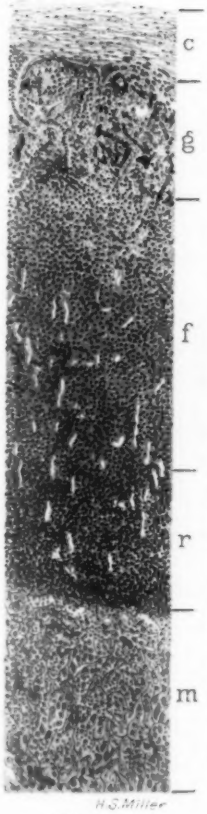
G.W. Henry

Fig. 1.
Dog XI.



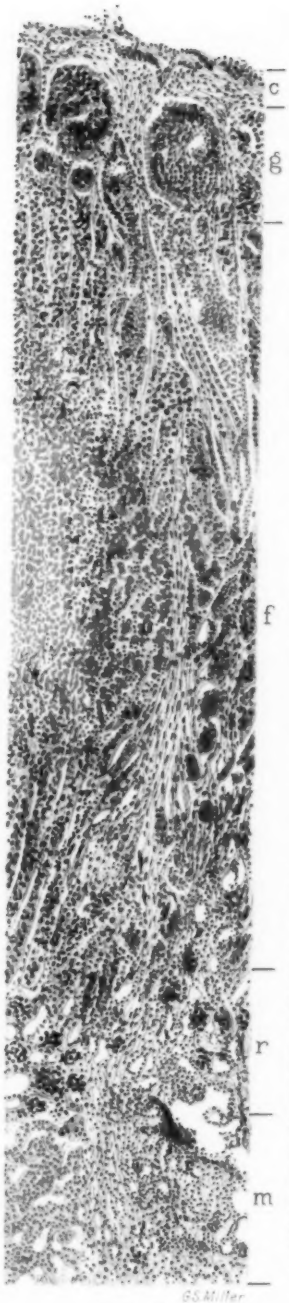
G.W. Henry

Fig. 2.
Dog XI.



H.S. Miller

Fig. 1.
Dog VIII.



G.S. Miller

Fig. 2.
Dog VIII.

G.W. Henry

Fig. 1.
Dog III.

PLATE I.

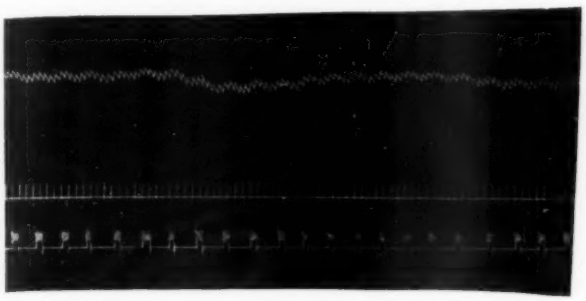


FIG. 3.—*Dog XXX.* **Adrenal insufficiency. Record made 24 hrs. before death.**

Pulse rate	81	per min.
Blood pressure	28	mm.
Respiration	18	per min.
Temperature	29°	C.

(Actual size.)

FIG. 5.—*Dog II.* **The entire left adrenal had been removed and all but this small fragment at the upper pole of the right adrenal. The animal was observed for more than one year subsequent to this operation. Death followed within a few hours after the removal of this remaining fragment of adrenal.**

Normal left adrenal.

Hypertrophied right adrenal.

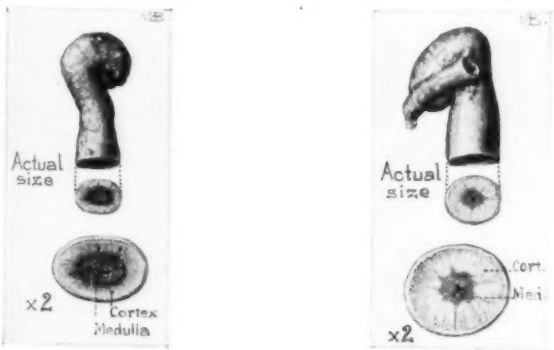


FIG. 4.—*Dog XI.* **Left adrenal removed at operation March 31, 1913. Right adrenal removed at autopsy April 14, 1913. Note hypertrophy of the cortex with an apparent decrease in size of the medullary portion.**

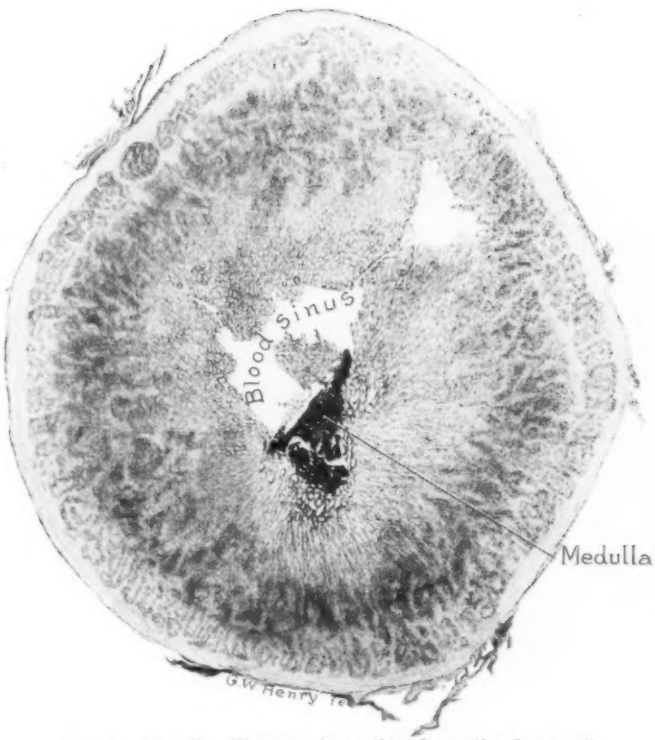


FIG. 6.—*Dog II.* **Microscopic section from the fragment of adrenal shown in the preceding illustration. Note hypertrophy of cortex; absence of hypertrophy of medulla. This section represents the maximum amount of medulla in the entire fragment. During the year of observation this animal developed normally.**

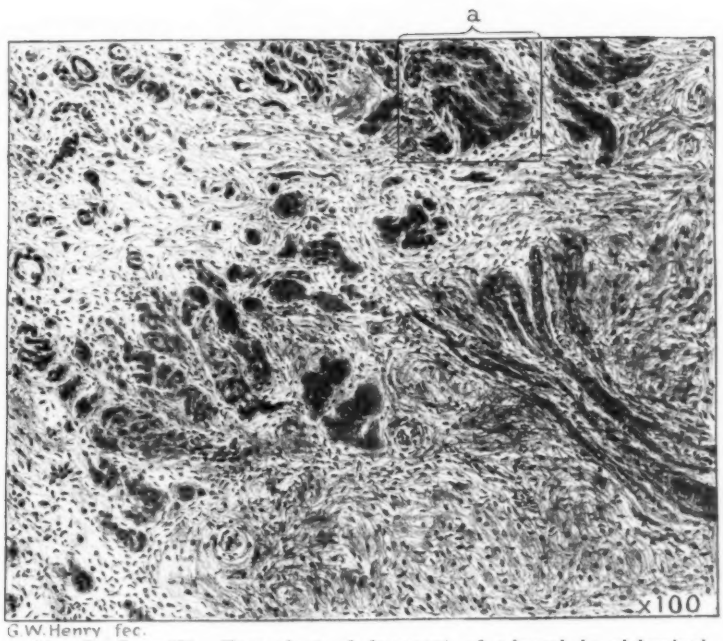


FIG. 7.—*Dog III.* Transplant of fragment of adrenal in abdominal wall; six months duration. Medulla cells have disappeared and only those of cortex remain.

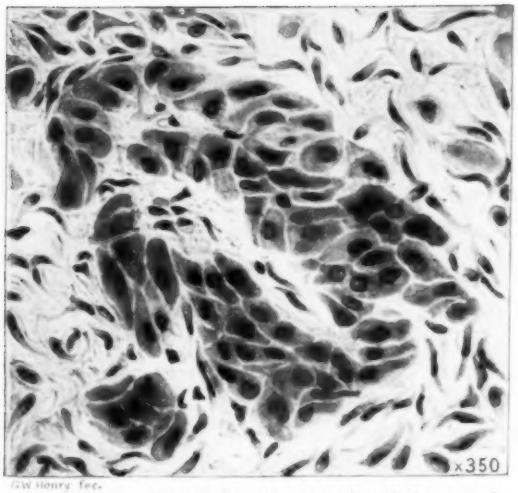


FIG. 8.—*Dog III.* Enlarged view of cells in preceding figure. These are lipoid-containing cells as shown by stain with Soudan III. This transplant was of no functional value since the animal succumbed a few hours after partial removal of remaining portion of adrenal.

FIG. 9.—*Dog II.* Photograph made one year after establishment of adrenal insufficiency. Has grown and developed normally.

A CLINICAL STUDY OF PRIMARY CARCINOMA OF THE FALLOPIAN TUBE.

By Cecil W. Vest, M. D., Baltimore.

Late Resident Gynecologist, The Johns Hopkins Hospital.

Before discussing the present views as to the incidence of primary malignant disease of the Fallopian tube, it may be of interest to refer to the ideas of gynecological authorities writing only a few years ago. In 1875 Schroeder,[87a] in his *Krankheiten der Weiblichen Geschlechtsorgane,* makes the following statement: "Carcinoma occurs in the tube never as primary and only rarely as an actual metastasis. In a case of medullary carcinoma of the right ovary, Scanzoni found the mucous membrane of the left tube infiltrated with cancer. It is evident, then, that cancerous destruction of the tubes is found only when the carcinoma from the ovary or the peritoneum, very seldom from the uterus, has involved the tubes in the degenerative process; and even then very often the tubes remain intact for a long period. Thus, in the presence of ovarian carcinoma, one not infrequently finds the tube free in the cancerous mass and it is evident that it has taken no part in the formation of the new tumor." This opinion is expressed in the various editions of this text-book which were issued during the subsequent fifteen years. In 1892 Zweifel [117b] made the following statement: "Carcinoma of the tube is a very rare disease, except when it occurs as metastases originating from the uterus. Carcinoma of the uterus, according to its method of extension, may finally involve the tube. To describe such a tumor as primary tubal carcinoma is to represent a common occurrence as if it were an interesting and rare one." One of the most comprehensive articles of the later works on this subject is to be found in Martin's [89] *Krankheiten des Eileiter.*

The first case of primary tubal carcinoma was published by Orthmann [72a] in 1888 and was followed by Doran's [22a] case in the same year and by Kaltenbach's [49a] in 1889.

With the development of surgery and the accompanying advancement in the study of the clinical and pathological material many other cases have been reported. Peham,[75] in 1903, collected 63 cases; Orthmann,[72b] in 1906, 84; Doran,[22d] in 1910, 100; and in 1911, Anduze-Acher [3] published his thesis, in which he had tabulated no less than 115 cases. Since then the number of reports has increased until, with those included in the present paper, 132 cases of primary carcinoma of the tube are to be found in the literature. Hence it is evident this condition is not so unusual as was formerly thought, and the gynecologist, when dealing with an adnexal tumor, must always take into consideration this possibility.

The two principal theories which have been advanced for the explanation of this neoplasm are those by Doran and Fearn and by Sänger and Barth.* These authorities are of opinion that a previous inflammation of the part is the provocative factor.

Doran and Fearn believe the carcinoma represents a malignant change which has taken place in a benign papillomatous condition consequent to an earlier salpingitis. Roberts's [87a] first case is a good example of this view. Upon macroscopic examination, the tube was seen to be filled with a papillary growth which at first was thought to be benign, but which microscopic examination showed to be malignant. The patient had had gushes of sanious fluid and a similar fluid was found in the tube.

Sänger and Barth's * theory is that the carcinoma arises upon the basis of a chronic, probably purulent, inflammation. This change does not occur in the presence of a recent condition, but after a long lapse of time, for the most part about the climacterium.

In view of the fact that an inflammatory condition was held to be an etiological factor in the causation of tubal carcinoma, an attempt was made to ascertain from the published cases whether or not any inflammatory changes in the pelvic structures were found at operation. Unfortunately in many cases the descriptions were meagre and in others no mention at all of this condition was to be found in the reports of the macroscopic or microscopic examinations, making it impossible to obtain any valuable data on this point. Again, when a small amount of inflammatory change was present at operation, it was often quite impossible to decide whether this had existed previous to the appearance of the new growth or was a result of its extension.

As to pregnancy, a record was found in 112 cases. Of these women 79 had become pregnant; 73 had been delivered of living children. Six patients had aborted and had had no other pregnancy. In all, 17 patients had aborted. Thirty-three were nulliparæ. Of the women who were delivered, 32 had had one child. Of the multiparæ, one patient had had seven children and another ten.

In an attempt to ascertain whether or not the patients had suffered from any tubal inflammation, the following deductions were made from the clinical data: In only a small number of the cases reported was there any history of a pelvic inflammatory disease. Since 70 per cent of the women became pregnant, it may be considered they were free from salpingitis; or if they were infected, the condition was either unilateral or not sufficient to prevent conception, or it had developed after delivery. Assuming that the 32 primiparæ (*i. e.,* 28.4 per cent of all the cases) suffered from a subsequent infection (the so-called one-child sterility) and that the 33 women without children were sterile from tubal inflammation, we should have a total of 57.7 per cent of the women who, at some time, had had a tubal infection. This leaves 42.3 per cent of the cases of primary carcinoma of the tube in which no previous inflammatory condition existed in the tube, and these

* Cf. Martin: Ref. No. 89.

cases must be explained in some other way. It is difficult to draw conclusions and this comparison of course is only theoretical and does not pretend to any accuracy, especially as so many conditions may enter into and modify the results. For instance, in the nulliparæ, the question of sterility of the male must be considered, while in the parous women the prevention of further conceptions must be considered. Again, whether the patient is married or single must be taken into account.

Thus:

Of 112 women,
79 or .....70.3% became pregnant.
Of the 79, 32 or .....28.4% had one child.
33 or .....29.3% did not become pregnant.
Considered sterile from inflammation..57.7%
Considered not to have had previous inflammation 42.3%.

In over 19,000 patients who have been treated in the gynecological wards of The Johns Hopkins Hospital, and in whose cases specimens from every piece of tissue removed have been examined microscopically, a large number showed inflammatory changes in the tubes. Many of these women had had the inflammation for many years, yet among this number there have been only four cases of primary tubal carcinoma. If a previous tubal inflammation is a primary factor in the causation of this condition, we should certainly expect a much larger proportion than four in a total of 19,000 cases. Hence we must conclude that inflammation of the tubes plays a minor rôle, if any, in the development of carcinoma of the uterine tubes.

Age.—Whether there was a pre-existing condition of inflammation in the tubes or not, it is obvious that the time of occurrence in these cases corresponds with that of malignancy in other parts of the body or with what may be termed the "cancer age." The ages are given in 127 cases. In sixty-eight, or 53 per cent of the patients, the condition occurred between the ages of 40 and 50, and it was observed thirty-eight times in the latter half of this period, the average age being 48.3 years. The youngest patient (27 years old) in this series is the one mentioned by Norris.[71] Pawlik's[74] patient, the oldest, was 70 years old, and had also borne the greatest number of children, having been delivered ten times.

The incidence at the various ages arranged in quinquennial periods is as follows:

27 to 30— 3 cases
30 to 35— 3 cases
35 to 40—11 cases
40 to 45—30 cases } 53 per cent of all the cases
45 to 50—38 cases }
50 to 55—19 cases
55 to 60—18 cases
60 to 65— 4 cases
65 to 70— 1 case

The types of carcinoma observed have been variously described and classified. Of these classifications Sänger and Barth's * was the first one published and is the one referred to by most authors. Two forms are differentiated:

(a) Papillary.
(b) Papillary-alveolar, which corresponds to adenocarcinoma of the uterus.

Friedenheim's classification is as follows:

1. Mucous-membrane carcinoma:
   (a) Papillary.
   (b) Papillary-alveolar.
2. Wall carcinoma.
   (a) Alveolar.

Falk's arrangement is:

(a) Benign papilloma.
(b) Malignant papilloma.
(c) Papillary epithelioma.

But although various classifications have been offered, as in dealing with cancer of the fundus uteri, it is better that one variety of carcinoma of the tube be considered. Although in the same specimen at one place a papillary and at another an alveolar arrangement will be seen, the papillary form is characteristic of this condition.

The middle and outer thirds of the tube are most often the site of the carcinoma and are altered in size. The uterine end is seldom changed, except as a result of the dilatation of the tube and proliferation of the neoplasm. The tube is filled with the cancerous mass and becomes distended, being retort or sausage-shaped and often assuming quite large proportions.

Changes in the tube wall are of interest, especially when compared with carcinoma of other hollow organs, in which extension through the outer wall is not unusual.

In malignancy of the tube definite changes may take place in the muscular layer. This portion may be thickened, as is seen in Case 2, or, as the result of the distention of the tube and pressure of the new growth, this layer may be much thinned, the wall being scarcely 2 mm. in thickness and macroscopically composed of a few muscle fibers and the peritoneal covering. Such a condition is seen in Case 3. In each instance there may be an invasion of the wall of the tube by the growth, but actual perforation of it by the neoplasm in its enlargement is rare. In Schäfer's[91] case and Spencer's[98] Case 2, the growth had extended through the peritoneal covering.

In the cases reported by Cullen[100] and Karakoz[46] each tubal mass measured 14 cm. in diameter, while in Gurd's[41] case it was 12 cm. The specimen removed in Stolz's[97] case is described as being as large as a fœtal head. The last-mentioned specimen presented quite an unusual picture, the uterine end being closed with carcinoma. The outer portion of the tube was buried in the cul-de-sac and was adherent. The fimbriated end was open.

As the distal end of the tube provides a way for the immediate escape of carcinoma cells, it is important to note the condition of the abdominal ostium when an early case is seen at operation. With the increase in amount of the tumor, the tube becomes filled with the carcinoma, which may partially or completely close the abdominal ostium. The ostium may also be closed as a result of inflammatory reaction. With

* Cf. Martin. Ref. No. 89.

carcinoma in the outer end of a tube whose ampulla is open, particles of the tumor can very readily be carried directly into the peritoneal cavity. When the end is closed immediate outward extension is prevented, unless there has been an escape of the cells before the end has become occluded. From our two cases seen at operation, there was proportionately more involvement of the peritoneum than of the lymphatic glands. This result was to be expected inasmuch as the carcinoma cells would naturally follow the line of least resistance. The peritoneal metastases occur for the most part by direct implantations.

In this way, traversing the path followed in transmigration of the ovum, these metastatic cells become lodged in the opposite tube. Herein doubtless lies the explanation of the large number of cases in which the growth is found to be bilateral. From the descriptions of the tubes in these cases, it would seem that the tumors were about the same size on each side and there is nothing to indicate which tube was primarily involved. Hence one is led to believe that the cells are dislodged and reimplanted early in the development of the primary growth.

The case reported by v. Rosthorn [87] is a good example of implantation in the opposite tube. A carcinomatous right tube was removed, but recurrences were noted in six months. A second operation became necessary and pelvic metastases were found. A small cancerous nodule was present in the left tube.

Glendening [39] found carcinoma cells in the lumen, in the subepithelial tissues of the lining folds and in the various layers of the tube. The sections were taken from the different parts of the tubes at operation from patients suffering from carcinoma of the stomach.

A longitudinal section of a carcinomatous tube shows it to be filled with a grayish-white granular mass. The tumor may form a homogeneous mass or in parts be raised in papillary or cauliflower-like growths. The central portion is often filled with a serohemorrhagic or purulent fluid. Areas of necrosis may be seen throughout the tumor in advanced cases.

As is to be expected, the new growth is found as often in the right tube as in the left, and it is interesting to note the large number of cases in which both tubes are implicated. About 26 per cent of the cases showed a bilateral malignant involvement, and in many of these cases there was no marked disproportion in the size of the tumors.

Thus, as regards the site, the right side was involved in 44; the left in 45; both sides in 36 cases. In two cases the growth is described as being unilateral; in four instances no mention is made of the side implicated.

Recurrence.—Carcinoma of the tube, while of fairly slow growth before the symptoms are pronounced, is highly malignant. The recurrences became evident soon after the operation, even in some cases in which it was thought that all traces of the disease had been removed. This is, of course, due to the extensiveness of the growth, metastases having been present in the peritoneal cavity and lymphatic system at the time of operation. The recurrences were primarily abdominal and took the form of large masses surrounding the vessels and nerves of the pelvis; there was also an enlargement of the peritoneal implantations and retroperitoneal glands with a consequent ascites. In showing how far removed metastases may be found, Rossinsky's [96] case is interesting. At the time of operation, a nodule was noticed in the left supraclavicular region, which after three months had become the size of an apple. It was excised and showed carcinoma. In v. Rosthorn's [87] case, a recurrence occurred in the vaginal incision, while in the second case reported by Spencer [96] the abdominal incision showed a new growth. Recurrent carcinoma has also been noticed in the uterus, bladder, vagina, liver, diaphragm, and omentum.

In the following table the patients had had a recurrence or had died from the disease:

DEATH OR RECURRENCE.

Within three months after operation	10
From the third to sixth month	11
From the sixth to twelfth month	24
During the second year	8
After the second year	5

Of the 132 patients, only four were well after five years and may be counted as cured: Wiesinger's [132] case after thirteen years, Zangemeister's [115] after eight, Benthin's [7] and Veit's [108] after seven. Five patients were well after three years and four after twenty-six months.

Symptoms.—The advanced condition found when the patient is referred for operation is probably to be explained by variation and irregularity in the occurrence of symptoms or failure to recognize those present early in the disease. Unfortunately the definite symptoms found in carcinoma of the uterus are often lacking where the tube is primarily implicated. There are, however, certain points associated with this condition which should be remembered and malignancy of the uterus or adnexa should be suspected when certain symptoms are present. Most commonly associated with this condition are a watery, vaginal discharge, often sanious, abdominal pain and menstrual disturbances.

At the onset of the disease the discharge, which is usually the first symptom noted, may be leucorrheal and blood-tinged in character, appearing as a continuous copious flow or in periodic gushes. It may be acrid and malodorous. Eglington's [38] case is of special interest, inasmuch as the discharge had been noticed for thirteen years. The carcinoma, of course, was not present during this time, but probably made its appearance in the year previous to operation, during which time the discharge was worse. The pain is often referred to the hypogastric region or is general throughout the abdomen and frequently is colicky in character. At other times it may be especially localized in one of the lower abdominal quadrants, but radiates to the upper abdomen, back and legs, later becoming constant and severe. Associated with these symptoms distention of the abdomen or a hypogastric tumor may be made out. The tumor may extend nearly to the umbilicus and be the first thing of which the patient complains. It is not unusual to have menstrual disturbances, such as menorrhagia,

metrorrhagia or a reappearance of vaginal bleeding after the menopause.

A profuse, blood-tinged discharge, abdominal pain with or without an abdominal tumor and menstrual disturbances are the characteristic features of this condition.

Loss of weight, cachexia, ascites, painful urination and defecation frequently appear late in the disease. When a patient gives such a history, though no abdominal tumor is to be made out, the presence of some malignant growth in the generative tract must be considered. The uterine curettings will doubtless be negative, but a careful pelvic examination should be made, if necessary under anæsthesia, when unilateral or bilateral thickening, if not an enlargement or tumor, is quite likely to be made out. When a patient describes such symptoms as have been enumerated and a pelvic tumor is found, it is better to attempt its complete removal through an abdominal incision rather than empty its contents through a pelvic puncture. A lateral tumor suspected of being a tubal carcinoma should not be emptied or examined by a vaginal incision. The tubal mass may be in the upper part of the pelvis or behind the uterus, filling the cul-de-sac. On palpation, it will be firm, rounded, transmitting a doughy or fluctuating sensation. Many tumors have been quite hard and tense, so that a diagnosis of myoma uteri was justifiable. In some instances the tumor was adherent. In a woman of middle age, the presence of a lateral tumor with ascites, even of short duration, should arouse a strong suspicion of malignancy. Ascites does not, as a rule, occur as early as in ovarian tumors and probably is more common in association with the latter growth. Pelvic metastatic nodules may be made out on vaginal or rectal examination. It is quite difficult, often impossible, to differentiate this condition from a malignant ovarian tumor, especially if metastatic nodules are present on the pelvic peritoneum. Such a tumor should, however, be considered malignant. In making a pelvic puncture, if blood-stained, watery fluid is obtained from a lateral tumor, the abdomen should be opened, a positive diagnosis made and a complete operation done if necessary. Care should be taken at operation lest what is thought to be a hydro- or haematosalpinx prove to be a tube containing a malignant growth, because if this is ruptured and its contents scattered throughout the lower part of the abdominal cavity the prognosis becomes infinitely worse.

That the possibility of the co-existence of tubal malignancy with an ovarian cyst must not be disregarded is shown by the first case of our series. Only after the operation for the removal of the cyst was the malignant tumor found. In Knauer's [52a] and Savor's [90] cases the cysts were known to have been present for eighteen years, whereas the immediate symptoms had only appeared within one year. Ovarian cysts were also present in the cases reported by Dirner,[21] Orthmann,[72d] Mériel,[56] Doran,[22d] Cullingworth,[16] Warneck [109] and Wiesinger [111] (third case). In Warneck's case the cyst was twisted twice on its pedicle.

The phases of rapidity of growth and metastasis are important and especially interesting from the clinical standpoint.

Nineteen patients were operated upon within four months from onset of symptoms.

Thirty were operated upon between the fifth and eleventh months.

Thirty-four were operated upon between the twelfth and the twenty-fourth months.

Eight in the third year.

Two in the fourth year.

As mentioned above, in one case certain symptoms were present thirteen years, and practically half of the patients allowed at least a year to elapse before an operation was performed. Thus it is seen that some of the tumors are not especially rapid in their growth. The delay in seeking medical advice is probably due to the fact that the patient thought the symptoms were natural or unimportant, and, the part involved naturally not permitting of inspection, the condition was disregarded, until the neoplasm had extended beyond the possibility of removal.

The meaning of these symptoms must be thoroughly recognized by the practitioner and a patient having such complaints must be submitted to a careful pelvic examination in order that the possibility of a uterine or tubal carcinoma may be excluded. It is of equal importance that the laity should know of these symptoms and their meaning, so that women having a profuse vaginal discharge, leucorrheal or blood-tinged, will understand the necessity of an early vaginal examination. In this way many cases of malignant disease of the uterus or tubes will be detected while there is still a great probability of a cure. When a woman complains of the symptoms here described and the uterine curettings show no malignant change, though nothing be made out on pelvic examination, carcinoma of the tube or a pre-cancerous lesion should be suspected.

The change in the tube known as hydrops tubæ profluens, or by the old writers as "dropsy of the tube," although not often seen, should be mentioned here. In this condition, the fimbriated extremity is closed and the lining membrane secretes a colorless, watery fluid. The hydrosalpinx may attain to quite large proportions, and become the size of a child's head or larger and palpable through the abdominal wall, before the contained fluid comes away. After the tubal contents have been expelled through the uterus and vagina, the tumor is much reduced in size. After refilling, the tube will again spontaneously empty itself. A discussion of the condition of hydrops tubæ profluens with the enumeration of several cases is contained in Edelberg's [28] article. In carcinoma of the tube the discharge is also frequently intermittent, which accounts for the association of these two conditions. In fact, some authors believe this form of hydrosalpinx to be a preliminary condition in the malignant tubal growth.

Prognosis.—So far as the rapidity of the growth, metastases and recurrence are concerned, carcinoma of the tube is quite comparable to carcinoma of the fundus uteri. The prognosis, however, owing to the advanced stage at operation, has been anything but encouraging. Only four patients are known to be well after five years. But should these cases be seen by the gynecologist in the early months of the symptoms, the hope

of a permanent cure should not be much less than in cases of uterine cancer or malignant growth of other operable viscera.

Treatment.—In carcinoma of the tube, a panhysterectomy and a double salpingo-oöphorectomy are indicated, together with a wide removal of the broad ligament on the side involved. In some instances, the existence of the carcinoma in the adnexa was not recognized until the material was studied microscopically. In several of these cases the abdomen was reopened and the complete operation performed.

Where the pelvic glands are enlarged and can be dissected out without unduly prolonging the operation, it may be of material advantage to remove them, if the retroperitoneal glands are not enlarged. But whenever there is a glandular involvement, as in uterine cancer, the growth has then doubtless extended beyond the hope of permanent cure by surgical aid. That the enlargement of the glands is due to inflammatory origin is much less probable than in uterine cancer.

In inoperable cases, when the carcinoma is causing pain from involvement of pelvic structures, as much of the mass as possible should be removed for the sake of temporary relief. This was done in one of our cases. The bisection operation was found to be the most advantageous method of removal.

As shown by Poirier,[m] the lymphatics for the tube and upper portion of the broad ligament are the same as those for the fundus, this area being supplied with two sets of vessels, which course between the folds of the broad ligament. The lymphatics leave the cornu of the uterus and as they go lateralward are situated to the inner side of the tube. In the infundibulopelvic ligament, they follow the course of the ovarian vessels and drain into the lumbar glands of the same side. This set of vessels and glands are most often involved in the extension of the tubal cancer through the lymphatics. The other lymphatics are directed anteriorly, following the round ligament and drain into the external iliac and the inguinal glands.

The lymphatics from the cervix and base of the broad ligament go to the lateral wall of the pelvis, to the external iliac and hypogastric glands and posteriorly to the lateral sacral and promontory glands.

In only a small number of cases did the inguinal glands show metastatic growths, the pelvic and retroperitoneal glands being the ones most generally involved.

Metastases to the diaphragm are not uncommon, but in only two instances are liver nodules mentioned. These are to be found in Fonyó's [n] first case and Wiesinger's [nn] second case. These two patients died on the second and third day, respectively, after operation, and the secondary growths were found at autopsy. Four nodules were found on the upper surface at operation in our Case No. 2. This is the only case noted in which liver metastases were observed at operation.

A table of the reported cases of tubal carcinoma was practically completed when Doran's [nnn] second paper was obtained. The table in this article completes one hundred cases which the author had collected from the literature. These articles (by Doran) are readily obtained and to avoid repetition the cases included in them have been omitted from the table here published. Only the cases which are not included by him and those that have appeared since are given. The cases of Spencer, Tate, Legg and Boxer are mentioned by Doran.

The fourth case which has been observed in The Johns Hopkins Hospital was reported by Schenck. An outline of this case is given in the table as Case No. III.

Demonstration of specimens of tubal carcinoma are reported by Amann,[3] Baisch [6a] and Penkert.[n]

Since the article was finished a detailed account of Baisch's case reported by v. Raabe,[6b] has been obtained and two cases have been reported. Baisch's case is as follows: Age 47; one child; menses regular until past three years, when flow became irregular; was increased in amount and lasted eight days. Flow has been increasing past two years.

Operation.—Hysterectomy, double salpingo-oöphorectomy. There was an intraligamentary ovarian cyst on the left side. The contents were evacuated, and during the removal of the pelvic structures the carcinomatous tube (left) was ruptured. No metastases were found at operation.

Macroscopic Examination.—Left tube, sausage shaped; contains carcinoma. Right tube, tortuous, hydrosalpinx.

Microscopic Examination.—Primary carcinoma. Papillary alveolar form with tubo-ovarian cyst. Metastases in uterus and ovary. Eleven months later, second operation for recurrence in abdominal wall, to left of median line. None in peritoneal cavity. Tumor, papillary alveolar in character. The clinical findings in this case are quite comparable to the condition found in Case I of our series.

Drutmann.[n] Patient, age 54; menopause four years. Had a blood-tinged, serous discharge for two years. A curetment was first done and from the material examined microscopically a diagnosis of carcinoma fundus uteri was made.

Operation (Döderlein).—Hysterectomy, double salpingo-oöphorectomy. Uterus contains three small subserous myomata. Ovaries atrophic. Tubes are normal except for a tumor the size of a pea in the portion of the right tube in the myometrium. On section, tumor was yellow in color and of butter-like consistency.

Microscopic Examination.—Tumor was a carcinoma of adenomatous type.

This case was operated on probably the earliest of any of the series here discussed.

Lipschitz.[n] Nullipara, age 44. Menses were irregular. Well until one year before operation, during which time patient had severe pain in back at menses. For about a year patient had abdominal pain on walking.

Operation.—Hysterectomy, double salpingo-oöphorectomy.

Macroscopic Examination.—Left tube normal. Outer part of right tube is dilated and contains a tumor the size of a hazel nut. Ampulla is closed. Uterus contains a small interstitial myoma.

Microscopic Examination.—The right tube contains tubercular inflammatory tissue, numerous papillary forms and carcinoma of the alveolar type. In the arrangement of the microscopic picture it is thought the carcinoma developed on the base of the old tuberculosis.

TABLE OF CASES.

Author.	Age.	Para.	Menses.	Symptoms.	Tube.	Operator and Operation.	Fimbriated end.	Metastases at operation.	Description.		Recurrence.
									Macroscopic.	Microscopic	
1. Roche.	44	2	Regular.	Metrorrhagia assoc. with abdominal pain.	Left.	(Boursier) Hysteromyomectomy. (Bisection) Double salpingo-oöphorectomy.	.....	.....	Large tubal tumors, cystic and brownish-red in color. Wall thin and tense. Left, size of small orange.	Carcinoma.	.....
2. Dandelski.	64	1 1 abortion.	Regular. Menopause at 48.	Pain in right side of abdomen and sacro-iliac region.	Right and left.	Hysterectomy. Double salpingo-oöphorectomy.	Left, closed. Right, adherent in pelvis.	.....	Left, tumor is in outer third of tube and is size of dove's egg. Right, white cauliflower-like mass.	Adeno-carcinoma.	Well, six months later.
3. Schenck.	53	4	Menopause at 50.	Pain in lower abdomen 2 yrs., assoc. with thin, blood-stain'd, offensive discharge.	Left.	Left salpingo-oöphorectomy.	.....	None.	Tube filled with new growth. Distal end dilated.	Adeno-carcinoma.	Well, 3 yrs. later.
4. Kundrat.	47	1 abortion.	Regular. Menorrhagia past 2 yrs.	Abdominal tumor 4 yrs. Rapid increase past 2 mos.	Right.	(Wertheim) Hysterectomy. Double salpingo-oöphorectomy.	Filled with carcinoma.	.....	Middle and outer parts filled with new growth. Abdominal end communicates with ovarian cyst.	Papillary carcinoma.	.....
5. Benthin.	40	1	Regular.	Menstrual flow foul-smelling past year. Abdominal pain six months.	Right.	(Pfannenstiel?) I. Right salpingo-oöphorectomy. II. Hysterectomy. Left salpingo-oöphorectomy.	Closed.	None.	Tube is retort-shaped and filled with a brownish, cauliflower-like mass.	Papillary alveolar carcinoma.	Well, after seven years.
6. Rossinsky.	44	3 2 abortions.	Regular.	Abdominal pain.	Left.	(v. Herff) Left salpingo-oöphorectomy.	Atresic, adherent to ovary.	Left supra-clavicular gland palpable.	Tube pear-shaped, cystic. Filled with papillary growth.	Carcinoma cylindrocellulare.	Supraclavicular nodule in 3 mos. size of an apple. Excised, showed carcinoma.
7. Cullen.	46	1 miscarriage.	Regular until last 3 mos. since when profuse. Past yr. profuse, leucorrheal discharge assoc. with blood and some odor.	Cramp-like pain in R. I. F. 2 yrs., left side 1 yr. Radiates to legs.	Right and left.	(Kelly) Hysterectomy. (Bisection) Double salpingo-oöphorectomy.	Right filled with new growth.	.....	Right tube distended and sausage-shaped, 14 x 12 x 10 cm. Left dilated to 4 cm., contains new growth in middle portion.	Adeno-carcinoma.	After 3 yrs.
8. Spencer.	64	Multipara.	Regular. Menopause at 48.	Greenish offensive discharge.	Left.	Hysterectomy. Double salpingo-oöphorectomy.	Closed.	Growth in upper portion of vagina.	Outer part of tube distended and contains a warty-like growth, the size of a pigeon's egg.	Carcinoma.	Died third day after operation.
9. Spencer.	35	0	Irregular and profuse.	Abdominal tumor 18 mos., pain 4 mos.	Left.	Left salpingo-oöphorectomy.	Closed.	Intestinal.	Distended and filled with a whitish, brittle growth.	Carcinoma.	Abdominal and in incision. Died after 1 yr.
10. Spencer.	58	1 3 abortions.	Regular. Menopause at 48.	Enlargement of abdomen, pain.	Left.	I. Left salpingo-oöphorectomy (marked ascites). II. 3 mos. later (Exploratory laparotomy).	Open.	None.	Tube forms outer wall of yellowish-white carcinomatous mass.	Papillary carcinoma.	3 months.

TABLE OF CASES.—Continued.

Author.	Age.	Para.	Menses.	Symptoms.	Tube.	Operator and Operation.	Fimbriated end.	Metastases at operation.	Description.		Recurrence.
									Macroscopic.	Microscopic.	
11. Walter-Tate.	52	3	Menopause at 48.	Yellowish, blood-tinged discharge. 2 yrs. assoc. with pelvic pain.	Right.	Bilateral salpingectomy.	.....	None.	Somewhat tortuous and cavity filled with soft friable growth.	Adeno-carcinoma.	Well, 27 mos. later.
12. Walter-Tate.	44	0	Regular until past 18 mos., since when flow has been scant.	Metrorrhagia for 3 mos. assoc. with pain in back and hips. Loss of weight.	Right and left.	Double salpingo-oöphorectomy. Appendictomy.	.....	Omental.	Right tube tortuous, wall contains plaques of growth. Left distended and contains new growth.	Columnar-celled carcinoma of both tubes. Metastases to omentum and right ovary.	Left hospital on 23rd day.
13. Legg.	42	—	Regular.	Abdominal pain and blood-stained discharge 2 years.	Right and left.	Double salpingo-oöphorectomy.	Left, closed. Right not made out.	Pelvic?	Left, tubo-ovarian cyst. Both tubes dilated and filled with yellowish-white carcinomatous mass.	Papillary carcinoma.	Well, 26 mos. after operation.
14. Boxer.	62	1	Regular. Menopause at 51.	Blood-stained, watery discharge for 6 mos. Was fetid and purulent. Cramp-like pains 3 weeks.	Right and left.	Hysterectomy. Double salpingo-oöphorectomy.	Left, closed. Right, communicates with tubo-ovarian cyst.	Omental and peritoneal.	Left, thickened and filled with brown tumor mass. Right, retort-shaped. Outer part filled with friable tumor mass.	Papillary alveolar carcinoma.	Well, 1 mo. Died after 6 mos.
15. Vignard.	42	1	Regular. Amenorrhea 6 mos.	Violent, radiating abdominal pain 3 yrs.	Left.	Double salpingo-oöphorectomy. 4 liters ascites.	.....	Infiltration of rectal peritoneum.	Left tube enlarged and filled with new growth. Right normal size. Some vegetations on outer surface.	.....	.....
16. Montgomery.	34	0	Regular.	Whitish discharge. Premenstrual pain. Profuse menses.	Right.	I. Right salpingectomy. II. Hysterectomy left salpingectomy.	.....	None.	Right, thickened in middle portion. Left, thickened.	Cylinder-celled carcinoma.	Well, 8 mos. after operation.
17. Weinbrenner	43	1 1 miscarriage.	....	For 1 year cramp-like abdominal pain followed by bloody, watery discharge.	?	Hysterectomy, salpingectomy.	.....	.....	Tube filled with carcinoma.	.....	.....
18. Tweedy.	30	1	Irregular.	Repeated hæmorrhages.	Right.	I. Right salpingectomy. II. Partial left salpingectomy; right oöphorectomy 3 wks. later	.....	.....	Fungating mass in tube.	Carcinoma.	.....
19. Eglington.	47	2	Menopause at 44.	Blood-tinged watery discharge 13 yrs. Worse past year. Increased on voiding.	Left.	Left salpingo-oöphorectomy.	Filled with friable carcinoma.	.....	Tube distended, retort-shaped.	Carcinoma. Some individual cells like sarcoma.	After 7 mos.
20. Gurd.	46	5	Regular.	Profuse, watery, slightly purulent discharge.	Left.	Left salpingo-oöphorectomy.	.....	.....	Tumor 12 x 8 x 7 cm. in middle of tube.	Carcinoma.	Well, 7 mos. after operation.

TABLE OF CASES.—Continued.

Author.	Age.	Para.	Menses.	Symptoms.	Tube.	Operator and Operation.	Fimbriated end.	Metastases at operation.	Description.		Recurrence.
									Macroscopic.	Microscopic.	
21. Fonyó.	50	2 1 abortion.	Regular, profuse flow. Menopause at 48.	Thin, watery, blood-tinged discharge for 2 yrs. Abdominal tumor.	Right and left.	Double salpingo-oöphorectomy.	.....	One nodule on upper surface of liver (autopsy).	Tubes enlarged and filled with solid white tumor. In part cystic degeneration.	Papillary carcinoma.	Died 2nd day. Peritonitis.
22. Fonyó.	56	3	Menopause at 51.	Abdominal tumor with pain 3 yrs. Thin, odorless discharge one yr.	Right.	Right salpingo-oöphorectomy.	.....	None.	Tube enlarged and filled with tumor, which for the most part is dark yellow in color.	Papillary alveolar carcinoma.	Well, after 3 yrs.
23. Karakoz.	55	2	Regular. Menopause at 50.	Profuse vaginal discharge. Retention of urine.	Left.	(Schirschow) Left salpingo-oöphorectomy.	Free.	.....	Tube sausage-shaped, distended. 14 cm. dia. in middle portion, cystic.	Papillary carcinoma.	.....
24. Bertino.	48	1	Regular. Menopause at 46.	Profuse white discharge. Small in amount at first. Abdominal enlargement. General weakness.	Right.	(Resinelli) Right salpingo-oöphorectomy.	.....	.....	Tube very much dilated. New growth attached to base of tube. Ovary free.	Papillary carcinoma.	.....
25. Wiesinger.	56	1	Menopause at 51.	Abdominal tumor and pain 3 years. Bloody, watery, odorless discharge. Severe pain.	Right.	(Dirner) Right salpingo-oöphorectomy.	.....	.....	Tube 5 cm. in dia. in middle portion. Nodules on outer surface. Tube filled with yellowish tumor, a few points showing coagulation necrosis.	Papillary carcinoma.	Well, 13 yrs.
26. Wiesinger.	50	2 1 abortion.	Profuse and painful for 2 years.	Watery flow after periods. Has noticed a tumor 2 yrs.	Right.	Right salpingo-oöphorectomy.	Open.	Omental and intestinal. Diaphragm and liver (autopsy).	Tube thickened and distended. Some areas of degeneration. Tube filled with carcinomatous mass. Small spaces filled with blood.	Papillary carcinoma.	Died 3d day. Sepsis.
27. Wiesinger.	40	0	Amenorrhea 2 mos.: previously profuse flow 5 mos. Stopp'd by curettement.	Sick 10 mos. Metrorrhagia 3 weeks before operation. Pain in back.	Right and left.	Double salpingo-oöphorectomy.	Closed.	.....	Right, retort-shaped and filled with carcinoma. Unilocular ovarian cyst. Left tube dilated.	Papillary carcinoma.	Well, 3 yrs. later.
28. Koenig.	No history.		....	.....	Left.	Hysterectomy. Double salpingo-oöphorectomy.	.....	Pelvic, peritoneal.	Left tube semi-cystic, 14 x 10 cm. adherent. Right hydrosalpin. Papillary growth over uterus and adnexa.	Carcinoma, (examined by Prof. Askanazy).	1 year. Exploratory laparotomy.
29. Boxer.	No history.		....	.....	.....	....	.....	.....	Both dilated and filled with new growth; retort-shaped. Bilateral ovarian cysts.	Carcinoma.	.....

Conclusions.—Primary carcinoma of the tube, while not common, is not as rare as has been supposed, and its possibility must be considered when a tumor lateral to the uterus is present. There have been four such cases in the Gynecological Department of The Johns Hopkins Hospital.

Definite symptoms are not regularly associated with the tumor, but one or more of the following are usually present: a watery, often blood-tinged, vaginal discharge; abdominal pain and induration on one side of the uterus; often a tumor is present. The discharge may be intermittent in character. Each tube is involved an equal number of times by the growth, while in about 28 per cent of the cases both tubes are involved.

If the condition is still confined to the tube a complete operation (hysterectomy, double salpingo-oöphorectomy) should be done; otherwise only palliative measures can be employed. A careful macroscopic examination (and microscopic, if necessary,) should be made before the abdomen is closed of every tubal tumor removed. In some cases the complete operation was done at a second laparotomy after the nature of the growth was discovered.

A microscopic examination should be made of a serohemorrhagic fluid obtained from a lateral tumor by pelvic puncture. Such a tumor should be considered malignant until proven otherwise.

Primary carcinoma of the tube may be present in association with an ovarian cyst.

The tumor is of a high grade of malignancy. At onset it may be of slow growth, but recurrence is soon noted after operation. In most cases the condition has been too far advanced for permanent relief when surgical aid was sought. Only four patients are known to be well five years after operation.

One of the patients of the cases here reported was colored.*

CASE No. 1.—Gyn. No. 11471. E. B., white, married, aged 58. Admitted August 15, 1904; discharged September 11, 1904.

Diagnosis.—Ovarian cyst (unilocular), left side; carcinoma of left tube.

Operation.—Salpingo-oöphorocystectomy (left).

Complaint.—Tumor in stomach.

Family History.—Negative.

Past History.—Always healthy. Menstruation normal. Menopause four years ago. Married twenty-three years; one child twenty years of age. Spontaneous birth. No miscarriages. No marked leucorrhœa.

Present Illness.—Patient noticed a tumor in the lower part of abdomen about six months ago. Since then it has been growing gradually. There has been no pain associated with the increase in the size of the abdomen. The patient has grown thinner about the face, arms and chest; feels weakened. Suffers much from shortness of breath. Bowels regular. Voids frequently, but without discomfort.

Physical Examination.—Mucous membranes, good color. No œdema about face. Lungs and heart negative. Abdomen much distended; measures 51 inches at its greatest girth. Flat note is obtained on percussion over whole abdomen. Oedema of feet and legs. No note on pelvic examination.

Operation.—(Dr. J. A. Sampson.) When the abdomen was opened through a median line incision, a considerable amount of free fluid escaped. A large intraligamentary ovarian cyst was found on the left side. It was very adherent. The cyst was punctured and the contents were evacuated. The left tube and ovarian cyst were removed. The uterus was normal. Convalescence was uneventful.

Macroscopic Description.—The specimen consists of the wall of an ovarian cyst, with the tube attached. The cyst is approximately the size of a child's head, measuring 15 cm. in diameter. The outer wall is rough; in places a few adhesions are attached. At the base of the tube and parallel to it is an indistinct line of demarcation, where the peritoneum was cut to effect the removal of the tumor.

The tube is attached to the upper portion of the cyst and measures 15 cm. in length; it is slightly distended throughout the distal half, in which part it has a semi-elastic feel. The fimbriated end is closed and no communication between the tube and cyst cavity is to be made out. The ampullar portion is 2 cm. in diameter and on section is seen to be filled with a grayish, granular material which has a vegetative appearance. The growth is attached to the lower half of the inner surface of the tube. The tube wall measures 2 mm. in thickness. The cyst is unilocular and is lined with a serous-like membrane which strips off readily. No metastatic nodules are seen on the inner or outer surface of the cyst. The cyst wall is 1 cm. in thickness.

Microscopic Examination.—Under the low power, the tumor is seen to be attached to the lower part of the tube. No folds are seen in the upper part of the tube, but the epithelium is intact. Springing from the base of the tube are pedunculated carcinomatous masses. The growth is papillary.

Under the higher power, numerous papillæ, or tree-like forms, are seen sweeping into the lumen from the base. As seen from the microphotograph, the middle part is quite large and from it run long strands of connective tissue to the tips of the terminal processes. The epithelial cells in these processes are, for the most part, small columnar with an irregular ovoid nucleus. The cells are arranged in single and double rows. Karyokinetic figures are seen. There is considerable round-cell infiltration about the base of the tumor.

The wall of the tube is of normal thickness, and here and there the upper portion of the muscularis is seen to be infiltrated by the tumor.

The daughter gave the following subsequent history concerning her mother:

After leaving the hospital in 1904 patient was in quite fair health for two years, having at times, however, some abdominal pain. After two years the pain became more severe and quite constant and there was, at times, swelling of the abdomen. These symptoms gradually increased, so that during the last four months of the patient's life she was confined to her bed. Three small nodules appeared behind the left ear during the latter months of her life. There was no vaginal discharge at any time and no symptoms to indicate any malignancy of the bowel.

She died April 22, 1909.

CASE No. II.—Gyn. No. 18859. A. S., black, widow, aged 44. Admitted November 12, 1912; discharged December 6, 1912.

Diagnosis.—Chronic pelvic inflammatory disease. Carcinoma of left tube. Myomata uteri. General peritoneal carcinosis.

Operation.—Hysteromyomectomy. Double salpingo-oöphorectomy.

Complaint.—Sharp pain in left side of the abdomen. Painful urination.

Family History.—Negative.

Past History.—Health always good until present illness. Menses began at twelve; regular until eighteen months ago. Until six months ago the periods increased, the flow some months being noticed twice, occasionally small clots being passed. The flow

* No note concerning the color of the patients was made when the histories were abstracted, but I do not recall any patient other than white being recorded.

during this time has been more profuse and very painful. Last period, November 12; the two previous, October 13 and September 21. The flow now lasts for four days instead of eight before the present illness. Married twenty-seven years. Seven children, the oldest 25, the youngest 13. One miscarriage at 29. Profuse leucorrhœa during the past year.

Present Illness.—For two months the patient has been having sharp, lancinating pains in the lower abdomen, localized more in the left lower quadrant, occasionally radiating to the pelvis. The pains have become more severe during the past month. Micturition has been painful for the past four weeks, associated with increased frequency, the patient voiding at times every five minutes. Pollakiuria worse at night. The bowels are constipated. No nausea, vomiting, or elevation of temperature. The patient has lost 20 pounds in the last two months.

Physical Examination.—The patient is a moderately well-nourished negress. Mucous membranes, fair color. Cervical, axillary and inguinal glands readily palpable. Heart, normal. Numerous fine râles heard throughout the bases of the lungs. Abdomen, symmetrical. Respiratory movements, normal. Wall, pendulous. The patient complains of pain when slight pressure is made over the lower half of abdomen, especially in the left quadrant. No masses are made out. Liver dullness normal. Spleen not felt.

Pelvic Examination.—There is a slight bloody discharge from the vagina. The cervix is lacerated. The fundus is enlarged to about twice the normal size; movements limited. A hard nodular mass, approximately 8 cm. in diameter, is felt attached to the fundus. The left tube and ovary cannot be differentiated in an inflammatory mass the size of one's fist and there are nodular masses felt throughout the pelvis. The right tube and ovary are slightly adherent. There is a great deal of tenderness in the fornices. Hemoglobin, 65 per cent.

Diagnosis.—Myoma uteri, chronic pelvic inflammatory disease.

Operation (Dr. C. W. Vest).—The abdomen was opened through a mid-line incision. The omentum was studded with pearly white nodules, varying in size from 2 mm. to 2 cm. in diameter. When the pelvis was exposed, the fundus with the left tube and ovary was bound up in a dense covering of adhesions. The right tube and ovary were slightly adherent. There was an interstitial myoma, 8 cm. in diameter, in the fundus. The adhesions about the left tube and ovary were released and these structures were delivered into the incision. The tube was markedly dilated. The fimbriated extremity was open; out of it projected a portion of the carcinomatous mass. The uterus and adnexa were removed by supravaginal hysterectomy. In order to obtain more room and facilitate the removal of the mass in the left half of the pelvis, the bisection operation was done, the right half of the uterus with the corresponding tube and ovary being removed first. Had the growth been confined to the tube the uterus and adnexa would have been removed together. The adherent tumor mass was taken out to give temporary relief from the severe pelvic pain. The liver was normal in size, but four metastatic nodules, the largest of which was approximately 3 cm. in diameter, were made out on its convex surface. The patient left the hospital on the 22d day in good condition.

Six weeks later she had symptoms of recurrence. There was no further enlargement of the cervical, axillary or inguinal glands. She died May 17, 1913.

Macroscopic Description.—The specimen consists of the uterus and adnexa. The uterus has been removed by bisection (supravaginal).

To each half of the uterus is attached the corresponding tube and ovary. The left half of the uterus measures 7 cm. in length. Its peritoneal covering is smooth over the anterior surface and fundus, but posteriorly is covered with dense, fibrous, shaggy adhesions. An interstitial myoma in the posterior portion of the uterus has been divided in the operation, the smaller part being attached to the left uterine half. The myoma is firm and has the usual characteristic appearance. The uterine wall is otherwise normal. It is 2 cm. in thickness. The uterine cavity measures 5 cm. in length. The endometrium is normal in appearance.

The left tube is markedly distended and rounded throughout the middle and outer parts. The fimbriated extremity is closed. It measures 13 cm. in length; 3 cm. in diameter in its middle portion, and 4 cm. at the fimbriated extremity. The peritoneal covering is fairly smooth over the inner half of the tube, the outer half, together with the inner side, being covered with coarse fibrous shreds.

Upon section, the lumen of the tube from within 2½ cm. of the uterine cornu to the fimbriated extremity is filled with a spongy, granular, branching growth which has a grayish-white appearance and is uniformly attached to the lining membrane of the tube. The musculature of the tube is intact and is hypertrophied. At no place is the growth seen to penetrate as deep as the outer portion of this part of the tube wall. Throughout the portion of the tube which contains the carcinoma the wall beyond the base of the growth varies in thickness from 6 to 9 mm. The uterine end of the tube beyond the growth is normal. It measures 7½ cm. in length; is free from adhesions and the fimbriated extremity is open. On section the lumen is normal. Excepting for a small Graafian follicle cyst at the inner pole, the right ovary is normal. At the hilum between the ovary and tube, two small nodules, each the size of a pea, are implanted on the peritoneum. These nodules are firm and their cut section has a pearly-white appearance.

Accompanying the specimen is a portion of the omentum, measuring 7 x 5 x 1½ cm. and of leather-like consistence throughout. Upon section, it is seen to be almost a solid mass of carcinoma.

Microscopic Examination.—Under the low power, the inner wall of the tube is seen to be the origin of an irregular, branching growth.

The musculature is thickened. Scattered throughout the specimen, a few places are seen where there is a beginning invasion of the muscle layer immediately below the margin of the growth.

The lumen is partially filled with tumor mass and detritus.

The higher power gives the papillary forms arising perpendicularly from the tube wall. Many have typical cone tree shape.

The stroma is similar to that already described. The epithelial cells of the branching processes, while of columnar shape, are slightly smaller than those of the other two cases, as are their nuclei, and are more closely arranged. For the most part they are arranged in a single layer.

The muscular layer is seen to be invaded by the growth in different places. There is marked round cell infiltration, especially in the muscle layer.

The same typical arrangement is to be seen in the omental metastases as is shown in the microphotograph. Between the end of the branching processes, masses of carcinomatous cells and detritus are found. The same picture is seen in the nodules in the right broad ligament.

The endometrium, myometrium, right tube and both ovaries are normal.

Case No. III.—Gyn. No. 19170. A. F., white, married, aged 47. Admitted March 21, 1913; discharged April 7, 1913.

Diagnosis.—Carcinoma of left tube. General peritoneal carcinosis.

Operation.—Left salpingectomy.

Complaint.—General weakness. Swelling of the abdomen.

Family History.—Negative.

Past History.—The general health has always been good. Menses began at thirteen; regular every four weeks; duration, seven days; moderate flow. No pain nor intermenstrual bleeding. No leucorrhœa. Last period, January, 1913; previous one, December, 1912. The periods have been getting more scant in the past year. Married twenty-three years. No children. No miscarriages.

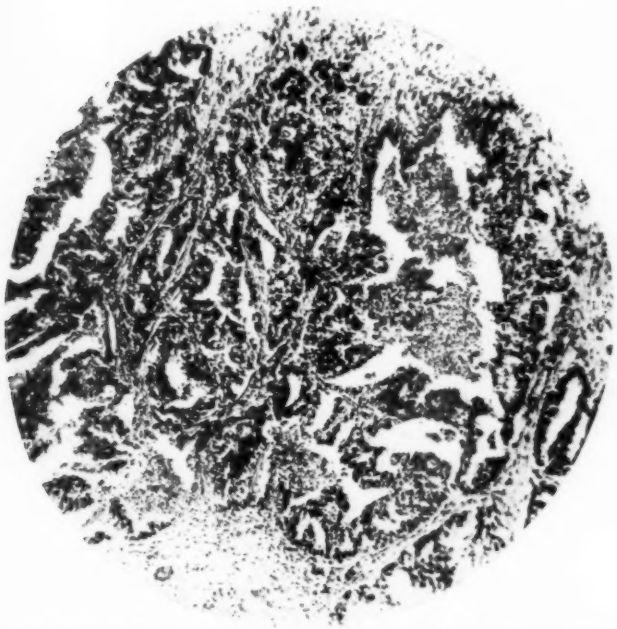
Present Illness.—About seven months before admission, patient noticed a fullness in the abdomen. The swelling has gradually

CASE No. II.—Gyn. No. 18859. Primary carcinoma of left tube. Metastases to omentum, base of right ovary and throughout the peritoneal cavity. Tube wall thickened. On account of the left-sided structures being densely adherent to the lateral wall of the pelvis and in the cul-de-sac the hysterectomy was done by the dissection method. Myoma in posterior wall of uterus.

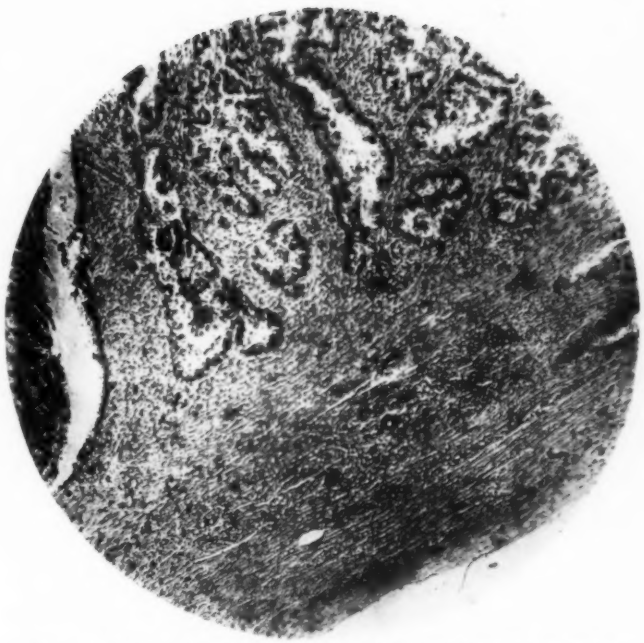
CASE No. II.—No. 18859 (a). Papillary or finger-like processes extending into the tube lumen which is seen to contain fragments of the growth and detritus.

CASE No. III.—Gyn. No. 19170. (a) Primary carcinoma of left tube. The growth distends the tube. The fimbriated end is open. (b) Longitudinal section showing carcinomatous mass, the central portion of which has softened and has been partially expelled. Tube wall thin.

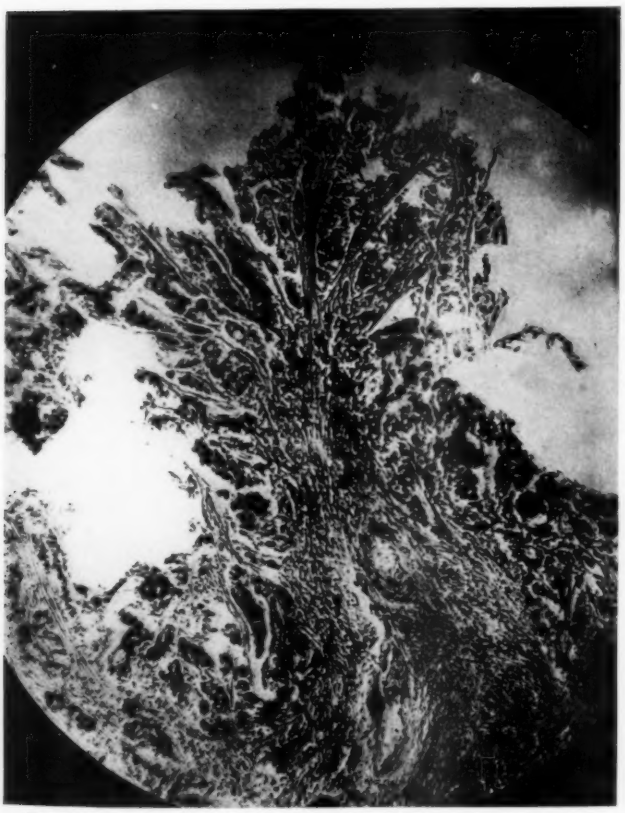
CASE No. I.—Gyn. No. 11471. Primary tubal carcinoma associated with an intraligamentary ovarian cyst. The tube is only slightly enlarged over normal.



CASE No. II.—No. 18859 (c). The characteristic arrangement of the primary growth is seen in the omental metastases.



CASE No. III.—No. 19170. Origin of typical branching forms. There is no invasion of the muscle structure. The entire thickness of this layer is shown.



CASE No. I.—No. 11471. Papilla arising from base of tube. The branching, tree-like arrangement of the extending processes is clearly defined.

CASE No. II.—No. 18859 (b). Section from the muscular layer of the tube showing the downward invasion of the growth.

increased until now the abdomen is quite symmetrically distended and prominent. Three months before admission she began to complain of general weakness and loss of weight. Four weeks ago she began to have quite severe pains throughout the abdomen and legs, associated with vomiting, slight elevation of temperature and chilly sensations. This condition persisted for over a week when she came under the care of Dr. John Folk of Bridgeport, W. Va., by whom she was brought to the hospital. The general weakness is becoming more marked. The bowels have been constipated for the past four months. No bladder symptoms nor metrorrhagia.

Physical Examination.—The patient is a fairly well-nourished woman. Mucous membranes, slightly pale. Heart, normal. The percussion note is flat below the sixth dorsal spine, extending around to the left anterior axillary line to the fourth interspace. The breath sounds in this area are of a blowing broncho-vesicular type and are accompanied by a few fine râles. The lungs otherwise are clear. The abdomen is full and rounded and there is considerable bulging of the flanks. Respiratory movements limited; no special areas of tenderness. In the left lower quadrant, an irregular nodular tumor, approximately the size of one's fist, can be felt. Definite ballottement is obtained. Definite movable dullness is made out. Liver dullness, normal. Spleen not felt. The cervical and inguinal glands are palpable.

Pelvic Examination.—The outlet is marital. The cervix is low in the vault and elongated; normal in outline. The fundus is enlarged to one-half again the normal size and is immovable. To the left of the fundus a tumor approximately 14 cm. in diameter is made out. The tumor is pedunculated and attached to the uterine cornu. It is quite tense and irregular in outline. The ovary cannot be differentiated. The right tube and ovary are adherent to the posterior surface of the broad ligament.

Rectal Examination.—Negative. Hemoglobin, 70 per cent.

Diagnosis.—Ovarian carcinoma. Ascites.

Operation (Dr. C. W. Vest).—March 22. The abdomen was opened through a median line incision and approximately 1500 cc. of clear yellowish fluid were evacuated. The latter part of the fluid was of a dull brownish color. On exploration of the pelvis the left tube and ovary were found to be adherent in an enlarged mass about 12 cm. in length. The fimbriated end was closed, but upon slight pressure on the tube there was an immediate escape of tapioca-like particles from the distal end. The right ovary was normal. The left ovary was adherent to the outer portion of the tube, but was normal in size and outline. The fundus, right tube and ovary were densely bound down by adhesions and peritoneal metastases. The right tube was slightly enlarged and its fimbriated extremity patent. There were peritoneal metastases throughout the pelvis, omentum and to the lower loops of the small intestine. The liver was normal.

The patient left the ward on the eighteenth day. The incision was well healed. There was at this time some dullness in the flanks, and on vaginal examination the indurated mass throughout the pelvis could be readily made out.

To Dr. Folk I am indebted for the following statement: The patient's condition was satisfactory and she was comfortable until November 1, when she became weaker. She had very little pain at any time. Death occurred December 18, 1913, nine months after operation.

Macroscopic Description.—The specimen consists of the left tube, which is markedly and quite evenly distended throughout its length and has a soft, doughy feel. It measures 15 cm. in length and 4.5 cm. in diameter at its middle portion. The peritoneum over the upper portion and sides of the tube is everywhere smooth, while about the base it is quite irregular and roughened by the presence of numerous hard, shot-like nodules. The tube is so distended with the tumor that portions of the carcinomatous mass are seen to project from both the uterine and fimbriated extremities. There is no evidence at any part that the tumor is about to break through the wall. When the tube is opened, it is seen to be filled with a grayish white, putty-like mass which, except over a small area at the junction of the inner and middle thirds of the tube on the outer convex surface, is attached to all parts of the inner surface of the tube. In the proximal third of the tube the tumor is of uniform solid consistency; the central portion of the remaining part of the tubal growth is soft, necrotic and shows a blackish discoloration. The part of the tumor overlying this area, which is conical shaped, the larger part being at the abdominal ostium, has been expelled, giving one the impression of the core having been removed.

In several places throughout the mass the tumor is trabeculated, coarsely granular and has a cauliflower-like arrangement. The muscular layer has been compressed by the growth, so that macroscopically the peritoneum is apparently the only covering of the tumor.

Microscopic Examination.—The wall is 3 mm. in thickness and is of quite uniform evenness throughout. Under the low power the musculature has the appearance of being pressed against the outer covering and has not been invaded at any point by the new growth. No normal tubal folds are seen. Arising from the inner side of the musculature, throughout the length of the section, are numerous papillary finger-like processes. Each one is seen to be made up of a central stroma portion, which has an epithelial covering. Although no definite form is to be made out, there is to each papilla a pseudo-tree-like arrangement.

From the sides of the lower part of a papilla a few projecting forms are given off, but it is throughout the upper part of the process that it is seen to divide into a cluster of smaller branches. Groups of the different terminal dendritic processes are in places massed together and apparently interlock. Although the base of each process is broader than the pedicle, the decrease in size is gradual until the larger branches are given off.

The central portion or stroma of the pedicle and larger branches make up the larger part of the structure. However, as the tube lumen is approached the papillary divisions are more numerous. In this portion of the growth there is a small amount of the central supporting structure and a large increase in the epithelial elements. Necrotic material is seen in the lumen.

Under the higher power, the lateral and end processes are seen to terminate in innumerable fine finger-like processes, which are usually interwoven with similar processes from many neighboring larger branches.

The cells covering the pedicle and larger divisions are large, elongated, and in places columnar. They are arranged in layers of two to four rows. The nuclei are large, round or ovoid and fill the lower half or two-thirds of the cell. The nucleoli are uniformly present. The cells about the terminal processes are approximately the size of those just described, but are arranged in single or double rows, usually the former. Karyokinetic figures are seen through the section. Numerous polymorphonuclear cells are seen as the lumen is approached.

The stroma is composed of long spindle shaped cells whose nuclei are oblong and stain deeply with hemotoxylin. There is considerable round cell infiltration throughout.

The cases here reported are from the service of Prof. Howard A. Kelly, whom I desire to thank for the privilege of placing them on record and for his assistance so generously extended to me.

To Dr. Thomas S. Cullen I wish to express my indebtedness and appreciation for his numerous suggestions and interest.

I wish also to thank Mr. Max Brödel for his drawings.

BIBLIOGRAPHY.

1. Amann: Zentral. f. Gynäk., 1907, XXXI, 490.
2. Andrews: Tr. Obst. Soc., Lond., 1903, XLV, 54.
3. Anduze-Acher: Thèse. Contribution a L'etude du cancer primitif de la trompe de Fallope. Toulouse, 1911.

4. Anufrief: Monatschr. f. Geburtsh. u. Gynäk., 1904, XX, 573.
5. Arendes: Dissertation. Ueber primares Carcinom der Tuben. Würzburg, 1900.
6. Baisch: a. Zentralbl. f. Gynäk., 1909, XXXIII, 976.
b. (v. Raabe) Beitr. z. Geburtsh. u. Gynäk., 1909, XV, 242.
7. Benthin: Arch. f. Gynäk., 1909, LXXXVII, 220.
8. Bertino: Ginecologia. Firenze, 1906, III, 424.
9. Bland-Sutton: a. Clin. J., Lond., 1904, XXIV, 1.
b. Tr. Obst. Soc., Lond., 1902, XLIV, 311.
10. Boldt: Med. Rec., 1897, LII, 66.
11. Boursier et Venot: Rev. de Gynéc et de Chir. Abd., 1901, V, 221.
12. Boxer: Monatschr. f. Geburtsh. u. Gynäk., 1909, XXX, 549.
13. Briggs: Tr. Obst. Soc., Lond., 1904, XLVI, 60.
14. Caraven et Lerat: Bull. et mém. Soc. Anat. de Paris, 1909, LXXXIV, 301.
15. Cullen: a. Bull. Johns Hopkins Hospital, 1905, XVI, 397.
b. Surg., Gynec. and Obst., 1910, XI, 75.
c. Tr. Am. Gynec. Soc., Phila., 1910, XXXV, 424.
d. Bull. Johns Hopkins Hospital, 1911, XXII, 20.
16. Cullingworth and Lockyer: Tr. Obst. Soc., London., 1905, XLVII, 263.
17. Cullingworth and Shattock: Tr. Obst. Soc., London., 1894, XXXVI, 307.
18. Dandelski: Dissertation, Primäres Tubencarcinom. Würzburg, 1907.
19. Danel: a. Jour. d. Sc. méd. de Lille, 1903, XXVI, 241.
b. Ibid., 1907, XXX, 121.
20. Delauney: Paris chirurgical, 1909, I, 15.
21. Dirner and Fonyó: Jour. Obst. and Gynec., Brit. Emp., 1903, II, 323.
22. Doran: a. Tr. Path. Soc., Lond., 1888, XXXIX, 208.
b. Ibid., 1889, XL, 221.
c. Jour. Obst. and Gynec., Brit. Emp., 1904, VI, 285.
d. Ibid., 1910, XVII, 1.
e. Allbutt and Eden's System Gynec., 2d Ed., 507.
23. Drutmann: Dissertation. Ueber einen Fall von primarem Tubencarcinom mit Uebergreifen auf die Uterus-Schleimbant. München, 1913.
24. Echardt: Arch. f. Gynäk., 1897, III, 183.
25. Edelberg: Gynäk. Rundschau, Berl. u. Wien, 1912, VI, 601.
26. Eglington: Jour. Obst. and Gynec., Brit. Emp., 1912, XXXI, 169.
27. Everke: Monatschr. f. Geburtsh. u. Gynäk., 1908, XXVIII, 461.
28. Fabozzi: Arch. Ital. di. Gyn., 1902, V, 124.
29. Falk: a. Therap. Monatschr., 1897, XI, 313.
b. Berl. klin. Wchnschr., 1898, XXXV, 554, 576.
30. Fearn: Martin's Krankheiten der Eileiter, 1895, 251.
31. Fehling: Lehrbuch der Frauenkrankheiten, 3d Ed., 306.
32. Fischel: Ztschr. f. Heilk., Prague, 1895, XVI, 143.
33. Fonyó: Zentralbl. f. Gynäk., 1913, XXXVII, 1317.
34. Frabricius: a. Wien. klin. Wchnschr., 1899, XII, 1230.
b. Zentralbl. f. Gynäk., 1898, XXII, 720.
35. von Franque: a. Ztschr. f. Geburtsh. u. Gynäk., 1902, XLVII, 211.
b. Monatschr. f. Geburtsh. u. Gynäk., 1905, XXII, 152.
36. Friedenheim: Berl. klin. Wchnschr., 1899, XXV, 542.
37. Gemmell: Jour. Obst. and Gynec., Brit. Emp., 1908, XIV, 31.
38. Glendening: Jour. Obst. and Gynec., Brit. Emp., 1910, XVII, 24.
39. Gosset: Ann. de Gynéc. et d'Obst., 1909, LXVI, 271.
40. Graefe: Zentralbl. f. Gynäk., 1902, XXVI, 1389.
41. Gurd: Canad. Med. Assn. Jour., 1913, III, 389.
42. Hannecart: Jour. de Chirurgie et Annales de la Société Belge de Chirurgie, 1901 (New Series 1), 580.
43. Hare: Boston Med. and Surg. Jour., 1905, CLII, 606.
44. Hofbauer: Arch. f. Gynäk., 1898, LV, 316.
45. Hurdon: Bull. Johns Hopkins Hosp., 1901, XII, 315.
46. Jacobson: Petersburg Geburtsh. u. Gynäk., Ztschr., 1898, XII, 1.
47. Macnaughton Jones: Practical Manual of Diseases of Women. 9th Ed., 1904, 678.
48. Kaltenbach: a. Zentralbl. f. Gynäk., 1889, XIII, 74.
b. Ztschr. f. Geburtsh. u. Gynäk., 1889, XVI, 357.
49. Karakoz: Russk. Vrach. St. Petersburg, 1912, XI, 471.
50. Kehrer: Monatschr. f. Geburtsh. u. Gynäk., 1908, XXVII, 327.
51. Keitler: Zentralbl. f. Gynäk., 1905, XXIX, 630.
52. Koenig: Gynec. helvet Genéve, 1912, XII, 1.
53. Knauer: a. Zentralbl. f. Gynäk., 1895, XIX, 574.
b. Ibid., 1901, XXV, 1211.
54. Kundrat: Arch. f. Gynäk., 1906, LXXX, 384.
55. Landau u. Rheinstein: Arch. f. Gynäk., 1891, XXXIX, 273.
56. Lecene: Ann. de Gynéc. et d'Obst., 1909, LXVI, 418.
57. LeCount: Bull. Johns Hopkins Hosp., 1901, XII, 55.
58. Legg: Jour. Obst. and Gynec., Brit. Emp., 1901, XVII, 38.
59. Lipschitz: Monatschr. f. Geburtsh. u. Gynäk., 1914, XXXIX, 33.
60. Lorrain: Bull. et mém. Soc. Anat. de Paris, 1909, LXXXIV, 235.
61. Low: La Gynécologie, 1903, 79.
62. Mercelis: New York Med. Jour., 1900, LXXII, 45.
63. Merder-voort: Zentralbl. f. Gynäk., 1905, XXIX, 597.
64. Mériel: Rev. mens. d. Gynéc. d'Obst. et de péd., 1908, III, 321.
65. Miknoff: Diagnostic et Traitment des Tumeurs de l'Abdomen, 1895, III, 564.
66. Montgomery: Jour. Am. Med. Assn., 1911, LVII, 1417.
67. Morinaga: Dissertation. Ueber maligne Erkrankung der Tube. Würzburg, 1903.
68. Müller: Dissertation. Würzburg, 1900. (After Dandelski.)
69. Münster: Deutsch. med. Wchnschr., 1901, XXVII, 111.
70. Novy: Monatschr. f. Geburtsh. u. Gynäk., 1900, XI, 1043.
71. Norris: Surg., Gynec. and Osbt., 1909, VIII, 272.
72. Orthmann: a. Ztschr. f. Geburtsh. u. Gynäk., 1888, XV, 212.
b. Ibid., 1906, LVIII, 395, 379.
c. Münch. med. Wchnschr., 1907, LIV, 1344.
d. Monatschr. f. Geburtsh. u. Gynäk., 1905, XXI, 571.
73. Osterloh: Zentralbl. f. Gynäk., 1896, XX, 809.
74. Pawlik: Tr. Obst. Soc., Lond., 1900, XLII, 6.
75. Peham: Ztschr. f. Heilk. Chirurgie, 1903, XXIV, 317.
76. Penkert: Zentral. f. Gynäk., 1909, XXXIII, 852.
77. Pilliet: Bull. et mém. Soc. Anat. de Paris, 1897, LXXII, 956.
78. Poirier: The Lymphatics. 1904, 164.
79. Quenu et Longuet: Rev. de Chir., 1901, XXIV, 742.
80. Rawls: Bull. Women's Hosp., New York, 1913, I, 9.
81. Ries: Jour. Am. Med. Assn., 1897, XXVIII, 962.
82. Roberts: a. Tr. Obst. Sc., Lond., 1898, XL, 189.
b. Ibid., 1899, XLI, 129.
83. Roche: Jour. méd. de Bordeaux, 1903, 152.
84. Rollin: Ann. de Gynec. et d'Obst., 1905, XXXII, 436.
85. Rose: Zentralbl. f. Gynäk., 1905, XXIX, 404.
86. Rossinsky: Thèse Bâle, 1910.
87. von Rosthorn: Ztschr. f. Heilk., Prague, 1896, XVII, 177.
88. Routier: Ann. de Gynéc. et d'Obst., 1893, XXXIX, 39.
89. Sänger: Martin's Krankheiten des Eileiter, 1895, 253.
90. Savor: Wien. klin. Wchnschr., 1895, VIII, 775.
91. Schäfer: Dissertation. Ein Beitrage zur caustik des primären Tuben carcinom. Leipzig, 1901.

92. Schauerstein: Mittheil. d. Vereines d. Aerzte. Steiermark, 1908. No. 2, 29.
93. Schenck: Detroit Med. Jour., 1905-6, V, 51.
94. Schroeder: a. Handbuch Krankheiten der Weiblichen Geschlechtsorgane. 1875, 324.
b. Ibid., 1890, 445.
95. Smyly: Dublin Jour. Med. Sc., 1893, XCV, 281.
96. Spencer: Jour. Obst. and Gynec., Brit. Emp., 1901, XVII, 30.
97. Stolz: Arch. f. Gynäk., 1902, LXVI, 365.
98. Stronganoff: Ann. de Gynéc., 1894, XLI, 332.
99. Tate: Jour. Obst. and Gynec., Brit. Emp., 1901, XVII, 35.
100. Tédenat: Arch. provincales de Chir., 1906, XV, 129.
101. Teubner: Dissertation. Leipzig, 1898.
102. Tomson: Jour. d'Obst. et Gynéc. de St. Petersburg, 1904, XVIII, 2018.
103. Tuffier: Ann. de Gynéc. et d'Obst., 1894, XLII, 203.
104. Tweedy: Tr. Roy. Acad. Med., Ireland, 1911, XXIX, 417.
105. Veit: Ztschr. f. Geburtsh. u. Gynäk., 1889, XVI, 212.
106. Vignard: Gaz. med. de Nantes, 1911, 526.
107. Violet: Lyon med. 1904. Ref. Zentralbl. f. Gynäk., 1905, XXIX, 1231.
108. Warneck: Nouvelles Arch. d. Obst. et de Gynéc., 1895, X, 81.
109. Watkins: Am. Gynec. and Obst., 1897, XI, 272.
110. Weinbreuner: Münch. med. Wchnschr., 1911, LVIII, 924.
111. Westermark and Quensel: Nord. med. Ark., 1892. Band II. Heft 1. No. 2.
112. Wiesinger: Gynäk., Rundschau, Berl. u. Wien, 1912, VI, 473.
113. Witthauer: Monatschr. f. Geburtsh. u. Gynäk., 1900, XII, 615.
114. Wynter: Tr. Path. Soc., Lond., 1891, XLII, 222.
115. Zangemeister: Beitr. z. klin. Chir., 1902, XXXIV, 96.
116. Zaretsky: Russian Monograph (after Doran).
117. Zweifel: a. Zentralbl. f. Gynäk., 1894, XVIII, 661.
b. Klin. Gynäk., 1892, 141.

THE NORMAL DIFFERENTIAL LEUCOCYTE COUNT.*

By SYDNEY R. MILLER, M. D.

(From the Clinical Laboratory of the Johns Hopkins Hospital.)

1. INTRODUCTION.

In 1911 Bunting[1] reported the results obtained in making differential leucocyte counts with Wright's stain on 25 normal individuals in the third decade of life. His figures differed from those almost universally accepted as the normal standard, especially in the low average percentage of polymorpho-nuclear neutrophilic leucocytes obtained and the correspondingly higher values for the mononuclear cells. These figures are well seen in Table 1, the figures of which are compiled from the most recent text books on clinical diagnosis and hematology.

TABLE 1.—AVERAGE PERCENTAGE VALUES OF LEUCOCYTES IN NORMAL BLOOD.

Author.	P. M. N.	P. M. E.	P. M. B.	S. M.	L. M.	T.
1. Pappenheim	70–75	2–4	0–1	20–22	2.....6	
2. Türck	70–75	2–4	.1–.5	22–25	1	1–4
3. Sahli ..... / Emerson..... / Ehrlich	70–72	2–4	.5	22–25	1	1–4
4. Morawitz	65–75	2–4	.5	20	5.....7	
5. Webster.....	65–75	2–4	.5	20–25	3.....5	
6. Wood.....	65–75	2–4	.5	22–25	1	2–4
7. Krause.....	65–70	2–3	.5	22–25	3.....5	
8. Naegeli	65–70	2–4	.5	22–25	3.....5	
9. Brugsch & S.....	65–70	2–4	.5	20–25	3.....5	
10. Morris.....	65–70	2–4	.5	22–25	3.....5	
11. Cabot.....	60–70	.5–4	.1–.5	20–40	1.....10	
12. Simon	60–70	1–4	.2–1	20–30	1.....6	
13. Bunting	50–60	.8–4	.4–1.8	30–40	.6–2	6–8

It is at once obvious from these figures that most observers still cling to the standards established in 1898, by Ehrlich, on counts made in Germany, and by the use of the stain that bears his name. These figures, moreover, give the impression that the individual cell values vary only within the designated limits, and that diagnostic conclusions may be safely drawn from slight variations from them. It is obvious that the gap between Ehrlich's and Bunting's figures is wide enough to make the interpretation of many leucocyte counts a matter of considerable speculation. Bunting found no neutrophile count as high as the Ehrlich minimum; "80% of the counts are lower than the minimum accepted by the majority of authors. On the other hand, the lymphocytes are above the maximum of the majority of the text books counts and the transitionals are also on the upper margin of the accepted normal. The other elements do not vary much from the usual figures."

Bunting briefly discusses the factors to which these variations may be attributed, such as the persistence of the lymphoid activity of adolescence, into the third decade, the tendency of the Wisconsin climate to cause chronic respiratory catarrh, and the use of a Romanowsky stain instead of the Ehrlich; but counts made upon older people, attempts to detect seasonable variations, and comparative studies made with the two stains failed to show the influence of any of these factors. The present report deals with the results obtained in an attempt to verify Bunting's work.

2. MATERIAL AND METHODS EMPLOYED.

As part of the routine blood work in the course in Clinical Microscopy, it is required of each third-year student that he first learn how to make blood smears. These smears are not acceptable unless they show relatively large areas wherein each cell is separate from every other one; each student proves for himself that this necessary evenness of distribution is secured only by the use of glassware carefully cleaned and polished. A technique is gradually acquired in the application of Ehrlich's and Wilson's stains. The student then makes differential counts on films, stained by each method, which have passed inspection by an instructor; 250 cells are counted on each

* Reported before the Johns Hopkins Hospital Medical Society, May 18, 1914.

smear, and from the percentages thus obtained are calculated the absolute values of the various leucocytes per cubic millimeter of blood as based on the student's total white blood count. These results, and the preparations from which they were obtained, are collected for final approval.

For the purpose of this study the stained films submitted by 50 students were selected at random. A differential count of 250 cells was then made by the author on each of the 100 preparations, and the results tabulated for comparison with those obtained by the students from the same slides. The analysis therefore is based upon a total of 50,000 cells.

The leucocytes were divided into the following six groups:

1. Polymorpho-nuclear neutrophilic leucocytes (P. M. N.)
2. Polymorpho-nuclear eosinophilic leucocytes (P. M. E.)
3. Polymorpho-nuclear basophilic leucocytes (P. M. B.)
4. Small mononuclears (S. M.) This group includes cells of the lymphocytic type with a relatively large deeply staining nucleus surrounded by a narrow rim of basophilic protoplasm. Cells are included here which are smaller than the average sized P. M. N. (10μ).
5. Large mononuclears (L. M.). This includes relatively few cells of the lymphocytic type the size of or larger than a P. M. N., the true "large lymphocytes," and also cells with a large round, oval, or slightly indented nucleus, eccentrically placed and poorly stained, surrounded by a considerable amount of protoplasm, the true "large mononuclears."
6. Transitionals. These are the largest cells encountered in normal blood, with deeply notched or saddle-bag nucleus, staining somewhat more deeply than No. 5 and surrounded by abundant protoplasm. The above descriptions apply to cells stained by the Wilson method, or any other of the numerous Romanowsky modifications. With Ehrlich's triple stain the specificity of the leucocytic granulations is sharply revealed, while all cells of the non-granular type are faintly stained and may be easily overlooked, especially if the differential counts are made by artificial light.

3. Analysis of Results.

The results secured in the manner above described can be appreciated best by an analysis of each cell type with reference to its average percentage value, absolute number per cubic millimeter and the group distribution of the counts.

Table 2.—Polymorphonuclear Neutrophilic Leucocytes.

Average Values.					Distribution of Counts.						
	Wilson Stain.		Ehrlich Stain.			Wilson Stain.		Ehrlich Stain.			
Counts made by	Percent.	Absolute Number.	Percent.	Absolute Number.	Number of Counts.	Students.	Author.	Students.	Author.	Total of All Counts.	Percentage Distribution of Counts.
Students	62.196	4805	66.448	5158	Over 80%	0	0	1	0	1	.5%
Author	60.846	4663	64.576	4955	70–80%	9	4	17	8	38	19.0%
Average	61.521	4734	65.512	5056	60–70%	27	34	21	31	110	55.0%
					50–60%	10	9	11	11	41	20.5%
					40–50%	3	6	0	0	9	4.5%
					Under 40%	1	0	0	0	1	.5%
Averages of all counts 63 516 Percent. 4895 cells per cmm.					Totals...	50	50	50	50	200	100%

These figures are interesting in several respects:

1. The averages as well as the group distribution of the counts are remarkably similar. This similarity holds good in the comparison of the counts made by one person with two stains, as well as with those similarly obtained but by numerous observers.

2. As was expected, the values obtained with Ehrlich's stain are slightly higher than those with Wilson's, though this applies practically only to the number of counts over 70%. Whether these values are real or are merely evidence of the fact that mononuclear cells were missed in these particular counts is impossible to state. Of the 100 Wilson counts, 87 lie below the Ehrlich minimum and 29 below 60%, the lowest limit given by any author save Bunting. With Ehrlich's stain 74 counts are below his minimum and 22 are lower than 60%. Of the total number of counts lying between 60 and 70%, 110 in all, exactly one-half were less than 65%; the highest count in the entire series was 82% and the lowest 33.6%, giving an arithmetical mean of 57.8%. This agrees within .8% with results recently published by Galambos,[2] based on a series of 100 counts made by the "Zahl-Kammer Method." In a recent study of 61 cases, von Torday[3] observed variations of 42.5% to 82.5%, giving an arithmetical mean of 65.1%. Observations made by Mehrtens[4] in California on 100 normal individuals resulted in an average of 56.5%. The possibility that some of the high counts in this series were due to the existence of colds at the time the counts were made, cannot be ruled out.

Table 3.—Polymorphonuclear Eosinophilic Leucocytes.

Average Values.					Distribution of Counts.						
	Wilson Stain.		Ehrlich Stain.			Wilson Stain.		Ehrlich Stain.			
Counts made by	Percent.	Absolute Number.	Percent.	Absolute Number.	Number of Counts.	Students.	Author.	Students.	Author.	Total of All Counts.	Percentage Distribution of Counts.
Students	2.544	205	2.704	218	Over 5%	5	7	6	8	26	13.0%
Author	2.552	214	3.012	235	4–5%	7	5	6	6	24	12.0%
Average	2.548	210	2.858	226	3–4%	4	5	6	4	19	9.5%
					2–3%	13	11	14	18	56	28.0%
					1–2%	12	11	8	8	39	19.5%
Averages of all counts 2.703 Percent. 218 cells per cmm.					Under 1%	9	11	10	6	36	18.0%
					Totals...	50	50	50	50	200	100%

The total average is 2.7%, despite the fact that 26 counts were over 5% reaching, in one instance, as high as 10.8%. These higher values are scarcely to be wondered at, however, in view of the relatively large number of students who come from regions in the south where parasitic infections are so prevalent. Five individuals failed to show any eosinophilic cells in either one or both of the smears examined. Of the total number of counts examined as many lie between 0-2% as between 2-4%, the figures given by 9 out of the 13 authors cited. Galambos (*loc. cit.*) observed in 65 normal individuals, variations between .48 and 10.5% with absolute values ranging from 39 to 911, while Mehrtens (*loc. cit.*) found an average of but .97%.

TABLE 4.—POLYMORPHONUCLEAR BASOPHILIC LEUCOCYTES.

Counts made by	Average Values. Wilson Stain. Percent.	Wilson Stain. Absolute Number.	Ehrlich Stain. Percent.	Ehrlich Stain. Absolute Number.	Number of Counts.	Distribution of Counts. Wilson Stain. Students.	Wilson Stain. Author.	Ehrlich Stain. Students.	Ehrlich Stain. Author.	Total of All Counts.	Percentage Distribution of Counts.
Students	.448	36	.452	35	Over 1%	7	9	5	9	30	15.0%
Author	.624	52	.529	43	.4–1%	24	33	28	28	113	56.5%
Average	.536	44	.490	39	0	19	8	17	13	57	28.5%
Averages of all counts	.513 Percent. 42 cells per cmm.				Totals...	50	50	50	50	200	100%

Little comment need be made on these figures which in all respects agree with the values universally accepted. The highest figure was 2.8%. It is apparently normal for a great many individuals to find no basophilic cells in counting a total of 500 leucocytes.

TABLE 5.—SMALL MONONUCLEARS.

Counts made by	Average Values. Wilson Stain. Percent.	Wilson Stain. Absolute Number.	Ehrlich Stain. Percent.	Ehrlich Stain. Absolute Number.	Number of Counts.	Distribution of Counts. Wilson Stain. Students.	Wilson Stain. Author.	Ehrlich Stain. Students.	Ehrlich Stain. Author.	Total of All Counts.	Percentage Distribution of Counts.
Students	21.39	1636	20.75	1562	Over 30%	6	7	4	4	21	10.5%
Author	24.07	1838	21.688	1858	25–30%	4	12	7	10	33	16.5%
Average	22.73	1737	21.219	1710	20–25%	17	15	15	16	63	31.5%
Averages of all counts 21.97 Percent. 1724 cells per cmm.					10–20%	23	16	23	19	81	40.5%
					Under 10%	0	0	1	1	2	1.0%
					Totals...	50	50	50	50	200	100%

Small mononuclear cells or lymphocytes are perhaps the easiest of all types to recognize, especially when stained by a Romanowsky method. In a comparative study such as this, the mononuclear elements in general furnish a fairly reliable index of the care with which the differential counts are made. It was among the non-granular cells therefore that discrepancies were expected, but found to be singularly infrequent. The total average of 21.9% tallies closely with the figures usually cited, but the wide limits of variation that a cell may show under presumably normal conditions is nowhere made more manifest than here. The highest figures with Wilson's stain were 45.2%, with Ehrlich's, 39.6%; the lowest 10.4% and 9.2% respectively. Of all the counts 41.5% are under the 20% mark and 58.5% above. Of these the majority lie between 20 and 25%. Bunting's average for the small lymphocytes alone, 23.3%, is hidden by reason of the fact that he combines in one average the sum of the averages of both small and large lymphocytes. It would seem that if it is necessary to make a separate large lymphocyte group at all, it would be wiser to report the values found for it separately.

This group, it will be recalled, includes two types of cells, namely true large mononuclears and lymphocytes the size of or larger than an average sized P. M. N. While clearly recognizing the separate existence of true large mononuclears and true large lymphocytes, there seems little to commend the practice of separating these two groups in making differential counts. True large lymphocytes normally occur in small

TABLE 6.—LARGE MONONUCLEARS.

Counts made by	Average Values. Wilson Stain. Percent.	Wilson Stain. Absolute Number.	Ehrlich Stain. Percent.	Ehrlich Stain. Absolute Number.	Number of Counts.	Distribution of Counts. Wilson Stain. Students.	Wilson Stain. Author.	Ehrlich Stain. Students.	Ehrlich Stain. Author.	Total of All Counts.	Percentage Distribution of Counts.
Students	9.392	700	6.368	490	Over 15%	5	4	3	3	15	7.5%
Author	8.388	664	7.72	585	10–15%	15	14	4	9	42	21.0%
Average	8.89	682	7.04	538	5–10%	19	24	22	26	91	45.5%
Averages of all counts	7.947 Percent. 610 cells per cmm.				Under 5%	12	8	21	12	53	26.0%
					Totals...	50	50	50	50	200	100%

numbers, and are frequently absent in a count of 250 cells. The arbitrary grouping of these two types of mononuclear elements employed here on the basis of a size index and not the finer shades of histological differentiation certainly minimizes confusion for the students and sacrifices none of the information to be derived from the differential counts themselves. The average, 7.9%, agrees quite closely with the sum of the averages of Bunting's large lymphocytes and large mononuclear groups, namely 10.8%. The limits of variation are again wide, ranging from 35.2% to .4%. One-fourth of the entire number of counts is less than 5%; one-half fall between 5 and 10%, and three fourths of the remainder between 10 and 15%.

TABLE 7.—TRANSITIONALS.

Counts made by	Average Values. Wilson Stain. Percent.	Wilson Stain. Absolute Number.	Ehrlich Stain. Percent.	Ehrlich Stain. Absolute Number.	Number of Counts.	Distribution of Counts. Wilson Stain. Students.	Wilson Stain. Author.	Ehrlich Stain. Students.	Ehrlich Stain. Author.	Total of all Counts.	Percentage Distribution of Counts.
Students	3.572	264	2.36	158	Over 4%	10	5	2	2	19	9.5%
Author	3.224	245	2.48	197	2–4%	30	27	30	35	132	61.0%
Average	3.398	255	2.42	178	0–2%	10	8	18	13	49	24.5%
Averages of all counts	2.884 Percent. 216 cells per cmm.				Totals...	50	50	50	50	200	100%

Probably because of the generally accepted idea that transitionals are senile forms of true large mononuclear cells, many authors group these two types together as may be seen in Table 1. There is further reason for this in that the total values for true large mononuclear and transitional cells for each individual are fairly constant, a low number of one type being usually associated with higher values for the other and vice versa. Morphologically, however, transitional cells are sufficiently distinct from all others to justify their separate grouping. Their increase assumes general significance in practically only one condition, namely, Hodgkins disease, a point particularly emphasized by Bunting.[4] The average of 2.8% agrees closely with those cited by Emerson, Ehrlich and Sahli, but differs quite outspokenly from Bunting's of 7.4%. Of the entire number of counts, only 19 were above 4%, with an upper limit of 12.4%. Both stains threw the majority of counts between 2 and 4%.

Since the completion of the work above described, the differential counts of the two successive classes, each of 90 students, have been subjected to analysis. The close parallelism throughout the first series between the results of the students and those

of the author made it seem unnecessary to apply similar comparative studies to the blood smears of the second and third series. Counts of 250 cells were made on each slide; in addition to the Wilson and Ehrlich smears, the students of the third series were required to make a count using Jenner's stain. The second analysis therefore was based upon a total of 450 counts representing 112,500 cells. A detailed study revealed the fact that the average values and group distribution of the various cells were practically identical with those before tabulated, even to the upper and lower limits which any type may exhibit. The net results therefore are presented in the composite tables (Tables 8, 9 and 10), which also include the values obtained in the first analysis. It will be seen that the final percentage averages, absolute numbers per cubic millimeter, and group distributions represent a total of 162,500 cells and 650 counts, made with three different stains upon 230 normal individuals in the third decade of life.

The analysis of the three composite tables (Tables 8, 9 and 10) reveals the following facts:

1. The average values for the ordinary P. M. N. as determined by three stains, including Ehrlich's, are lower than the usual standards, and the cells show limits of variation much wider than is generally believed. The figures are consistently higher with Ehrlich's stain. It is probable, however, that this may be attributed in part to the omission of mononuclear cells, particularly of the large variety; these stain faintly at best with Ehrlich's stain, suffer first in the fading of the smears, and are extremely hard to detect at all by artificial light. While it is true that the neutrophilic granules are often unstained by Romanowsky methods, the cells in question

TABLE 8.—THE AVERAGE PERCENTAGE VALUES OF THE LEUCOCYTES IN NORMAL BLOOD.

	P. M. N.			P. M. E.			P. M. B.			S. M.			L. M.			T.		
	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.
1st Series—Students	62.196	66.448	.....	2.544	2.704	.....	.488	.452	...	21.39	20.75	...	9.392	6.368	.....	3.572	2.36	.....
1st Series—Author	60.846	64.576	.....	2.552	3.012	.....	.624	.529	...	24.076	21.668	...	8.388	7.720	.....	3.224	2.48	.....
Class of 1913	61.54	65.82	.....	2.49	2.60	.....	.5	.42	...	24.42	21.92	...	7.04	6.36	.....	3.44	2.66	.....
Class of 1914	64.49	67.51	64.51	2.66	2.78	2.79	.83	.88	.82	22.34	21.50	22.	7.46	5.91	7.59	3.25	2.38	2.59
Averages	62.268	66.088	64.51	2.561	2.774	2.79	.61	.57	.82	23.306	21.459	22.	8.07	6.589	7.59	3.371	2.47	2.59
Total average of 650 counts	64.288			2.708			.633			22.255			8.083			2.81		

TABLE 9.—THE AVERAGE ABSOLUTE NUMBERS OF THE LEUCOCYTES, PER CUBIC MM. AND TOTAL WHITE COUNTS.

	Number of Individuals.	Limits of Variation in the Leucocyte Counts.	Average of all Leucocyte Counts.	P. M. N.			P. M. E.			P. M. B.			S. M.			L. M.			T.		
				Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.
1st Series—Students	50	5200–11,000	7400	4805	5158	.....	205	218	...	36	35	...	1636	1562	.....	700	490	...	264	158	...
1st Series—Author	50	Ditto	Ditto	4663	4955	.....	214	235	...	52	43	...	1838	1858	.....	664	585	...	245	197	...
Class of 1913	90	5000–9800	7200	4430	4739	.....	180	204	...	36	30	...	1758	1578	.....	506	458	...	238	191	...
Class of 1914	90	4600–10,200	7300	4708	4928	4710	193	202	203	61	64	59	1630	1560	1606	545	431	554	237	174	189
Total	280	Averages..	7300	4652	4945	4710	198	215	203	46	43	59	1723	1640	1606	606	491	554	246	180	189
			Average of all 650 Counts..	4769			205			49			1656			550			205		

TABLE 10.—THE GROUP DISTRIBUTION OF 650 DIFFERENTIAL COUNTS MADE ON 230 NORMAL INDIVIDUALS.

P. M. N.		P. M. E.		P. M. B.		S. M.		L. M.		T.	
Percentage Values.	No. of Counts.	Percentage Values.	No. of Counts.	Percentage Values.	No. of Counts.	Percentage Values.	No. of Counts.	Percentage Values.	No. of Counts.	Percentage Values.	No. of Counts.
Over 80%	4	Over 5%	74	Over 1%	137	Over 30%	57	Over 15%	18	Over 4%	79
70–80%	135	4–5%	65	.4–1%	351	25–30%	124	10–15%	101	2–4%	413
60–70%	302	3–4%	72	0	162	20–25%	243	5–10%	359	0–2%	158
50–60%	126	2–3%	207	.....	.....	10–20%	219	Under 5%	172	.....	.....
40–50%	21	1–2%	125	.....	.....	Under 10%	7	.....	.....	.....	.....
Under 40%	2	Under 1%	107	.....	.....	.....	.....	.....	.....	.....	.....
Total	650		650		650		650		650		650

rarely fail of recognition by reason of the shape of their deeply stained nuclei. Of the total number of counts with all stains lying between 60 and 70%, slightly more than one-half were under 65%.

2. The eosinophiles and basophiles differed scarcely at all from the usual normal values.

3. For the small mononuclear cells practically the same figures were found as those given by most authors. The total average agrees within 1% of that observed by Bunting for the small lymphocytes alone. With all stains the cells show a considerably wider range than is usually taught, and as one is led to suppose by the figures generally given. The values are slightly lower with Ehrlich's stain.

4. The arbitrary group of large mononuclears including, as has been stated, two types of cells, shows an average higher than that usually cited, namely 8.08%. Bunting's figure. 1.6% represents probably the prevalence of the true large mononuclear cells. The total of his averages for the lymphocytes, both large and small, and large mononuclears, is 34.7%; that in this series, 30.3%.

5. Finally as regards the transitional cells, it is evident that the great majority of the counts with all stains lie between 2 and 4%, the values again tending to be somewhat lower with Ehrlich's stain. The average for the entire series is considerably lower than Bunting's.

6. As regards the relative values of the three stains used, the following points may be cited:

a. Ehrlich's stain is a good granular and poor nuclear stain, and tends to give higher values for the P. M. N. and lower figures for the mononuclear elements.

b. Wilson's stain is a poorer granular and a better nuclear stain than Ehrlich's and gives therefore figures somewhat the reverse of (*a*).

c. Jenner's stain is a better granular stain than Wilson's and a better nuclear stain than Ehrlich's. The values obtained with this stain therefore tend to lie between those of the other two.

4. General Discussion.

It is rather singular that so few studies of the normal blood picture have been made since the pioneer investigations of Ehrlich and Einhorn. The matter is one of great importance, however, especially since slight quantitative changes in the differential formula are constantly being cited as possessing diagnostic value in a great number of conditions. Particularly is this true with reference to the mononuclear elements. Their increase is regarded by many as of significance in tuberculosis, typhoid fever, measles, mumps, lues, pellagra, malaria, scurvy, Grave's disease, myxoedema, tabes dorsalis, achylia gastrica, dementia præcox, Addison's disease and a host of others. But it is imperative to know within what limits a cell may reasonably vary under normal conditions in order to be able to interpret its abnormal increase or decrease. The older values for the non-granular elements were determined by staining methods which did not bring out the mononuclear cells as do more modern ones. Moreover, in all likelihood there exist quantitative differences in the leucocytic formula of normal individuals due to a number of local conditions, such as altitude, climate, humidity, and so on, as well as purely individual factors. Baer and Engelsmann,[8] for instance, confirm the work of Staubeli [7] concerning the leucocytic formula in higher altitudes, all agreeing that whereas the large mononuclears and transitionals show no change from their lowland values, the lymphocytes undergo an absolute and percentage increase at the expense of the neutrophilic cells. During a number of purely physiological processes such as exercise, sleep and during the digestion particularly of fats and carbohydrates, numerous observations have shown the tendency for mononuclear elements to be increased. A great number of clinical observations have tended to prove that the influence of various internal secretions tend to raise the mononuclear content of the blood, especially in those individuals who show a predominance of vagotonic symptoms. Galambos (*loc. cit.*), in the study of 100 normal individuals, found a total average of the mononuclear elements of 39.5% with variations from 18 to 67% of the total white count. He goes so far as to state that there may be as many lymphocytes in health as there are in certain diseases, leukemia excepted. von Torday (*loc. cit.*), in 61 cases, saw variations of 13 to 40.4%; and Mehrtens (*loc. cit.*), in 100 cases studied in California, secured an average of 37.45%. As the result of the examination of 110 cases, Huhle [9] concludes that only counts which repeatedly show a lymphocytosis of over 35 to 40% are of any importance. That local climatic factors and other physical forces not exactly known exert a determinative influence upon the leucocytic formula is nowhere better shown than in the basin of the Great Lakes, in this country, where not only in human individuals, but throughout the animal kingdom, there is a tendency to lymph-adenoid hyperplasia manifested during life in the blood and frequently in the glandular system, and at autopsy by the finding of enlarged glands and spleens which average a greater weight than in other sections of the country.

Even the total white count is subject to a wider variation than is generally conceived. The figures in this series shown in Table 9, are in accord with those of Galambos (*loc. cit.*) who finds an average of 7413 with extremes lying between 3500 and 12,500. All the high counts in this series, with one exception, were associated with values for the P. M. N. below 65%. Galambos was able to show that in the same individual, on the same day, the leucocytes may vary 100%. He found no striking difference between the two sexes, nor was he able to disclose any marked or constant post-prandial leucytosis. Where one did occur, the mononuclear elements were most affected.

5. Conclusions.

From the work cited and results herewith recorded, the following conclusions may be drawn.

1. The total leucocyte count and differential formula in normal individuals are subject to relatively wide variations, which must be considered in the interpretation of studies made upon the bloods of individuals presumably suffering from abnormal conditions.

2. The interpretation of any differential count should be based upon:

a. A knowledge of that particular individual's normal blood picture, when possible.

b. The average values for the locality in which that individual resides.

c. A consideration of those factors peculiar to the individual which might modify that particular blood.

3. Differential leucocyte counts should always be reported in terms both of percentage and absolute numbers per cubic millimeter, and in all cases, where possible, more than one differential count should be made, especially in borderline cases in which slight changes are to be regarded as of diagnostic or prognostic value.

4. The tendency to ascribe a diagnostic value to lymphocytosis is probably overdone. Only when the mononuclear elements constantly exceed the average percentage, absolute values and upper limits of variation (35-40%) for the community and when all modifying factors are considered, should one attempt to draw valuable conclusions from the figures obtained.

BIBLIOGRAPHY.

1. Bunting: Am. Jour. Med. Sc., CXLII, 1911, 698.
2. Galambos: Folia Haemat, XIII, 1912, 153-176.
3. von Torday: Virchow's Archiv, CCXIII, 1913, 529.
4. Mehrtens: Arch. Int. Med., XII, 1913, 198.
5. Bunting: Bull. Johns Hopkins Hosp., XXV, 1914, 177.
6. Baer and Engelsmann: Deutsch. Arch. f. klin. Med., CXII, 1913, 56.
7. Stäubli: Verhandl. des deutschen Kongresses f. inn Med., 1910.
8. Huhle: Deutsch. Arch. f. klin. Med., CXIII, 1914, 455.

THE QUARTER CENTENNIAL ANNIVERSARY OF THE OPENING OF THE JOHNS HOPKINS HOSPITAL AND THE TWENTY-FIRST ANNIVERSARY OF THE OPENING OF THE MEDICAL SCHOOL

Will be observed by appropriate exercises beginning October 5, 1914, and continuing during the week.

The exercises upon Monday, October 5, 9.30 a. m. to 12 m., are to be especially arranged for by the Training School for Nurses and will be announced later.

Upon Monday at 3.00 p. m., the formal opening meeting will be held at the Lyric, Judge Henry D. Harlan, President of the Board of Trustees of the Johns Hopkins Hospital will preside, and there will be addresses by President-Elect F. J. Goodnow, Dr. Wm. H. Welch, Dr. Henry M. Hurd, Miss M. Adelaide Nutting and Dr. Winford H. Smith.

In the evening there will be dinners of the former Medical Officers of the Hospital and of the Alumnæ of the Training School for Nurses.

Upon Tuesday, October 6, 9.30 a. m. until 12 m., papers upon medicine by former members of the staff will be presented in the Medical Amphitheatre. Gynecological operations in the Surgical Amphitheatre 10 a. m. until 1 p. m. Papers and demonstration by members of the Obstetrical Staff in the Surgical Lecture Room from 12 m. to 1 p. m.

Luncheon at the Hospital from 1 to 2.30 p. m.

At 2.30 p. m. there will be visits to the Harriet Lane Home with Dr. Howland, Professor of Pediatrics, and to the Henry Phipps Psychiatric Clinic with Prof. Adolf Meyer, Professor of Psychiatry.

A demonstration of nurses' work in the Medical Amphitheatre from 4 to 5 p. m.

From 4.30 to 5.30 a lecture on the Herter Foundation by Dr. Thomas Lewis of London.

A dinner in the evening by the Alumni of the Medical School.

Wednesday, October 7, from 9.30 a. m. to 12 m., surgical operations in the Surgical Amphitheatre. From 11 a. m. to 1 p. m. Urological Surgery in the Surgical Amphitheatre.

1 p. m., Luncheon.

At 2.30 p. m. visits to the Medical Laboratories.

4.30 p. m. Dedication of the Hewetson Medallion and a Tablet to Deceased Residents.

On Thursday, October 8, 9.30 a. m. to 12 m. papers on Pathology in the Medical Amphitheatre. The entire forenoon will be given over to papers by former members of the Pathological Staff.

1 to 2.30 p. m. Luncheon.

4:30 p. m., second Herter Lecture by Dr. Lewis.

In the evening, Class Dinners.

Third Herter Lecture will be given on Friday, October 9.

During the Anniversary Week laboratory demonstrations will be given in the laboratories of the Medical School as follows:

In the Anatomical Laboratory, By Prof. Mall and the Anatomical Staff.

In the Physiological Laboratory, By Prof. Howell and the Physiological Staff.

In the Pharmacological Laboratory, By Prof. Abel and the Pharmacological Staff.

The exact dates and hours of such demonstrations will be announced in the final program.

PROGRAMME

MONDAY	TUESDAY	WEDNESDAY	THURSDAY
Nurses' Day	9.30–12 Medicine (Medical Amphitheatre) 10–1 Gynecology (Surgical Amphitheatre) 12–1 Obstetrics (Surgical Lecture Room)	9.30–12 Surgery (Surgical Amphitheatre) 11–1 Urological Surgery (Surgical Amphitheatre)	9.30–12 Pathology (Medical Amphitheatre)
	Luncheon	Luncheon	Luncheon
Opening Meeting (The Lyric) 3.00 Judge Henry D. Harlan, presiding Addresses: Pres. F. J. Goodnow Dr. Henry M. Hurd Dr. Wm. H. Welch Miss Adelaide Nutting Dr. W. H. Smith Music	2.30 Pediatrics Dr. Howland 2.30 Psychopathic Wards Dr. Meyer 4.30 Herter Lectures Dr. Lewis 5.00 Garden Party (Hospital Lawn)	2.30 Visits to Laboratories Drs. Abel, Howell and Mall 4.30 Dedication Medallion: Dr. Hewetson Tablet to Deceased Residents	2.30 Inspection James Buchanan Brady Urological Institute 4.30 Herter Lectures Dr. Lewis
Dinners Johns Hopkins Hospital Residents Nurses	Dinner Medical Alumni	Class Dinners	

THE HERTER LECTURES FOR 1914.

The Herter Lectures will be given in connection with the Quarter Centennial Anniversary of the Opening of The Johns Hopkins Hospital and the Twenty-first Anniversary of the Opening of the Medical Department of The Johns Hopkins University, upon Tuesday, Thursday and Friday, October 6, 8 and 9, 1914, at the Physiological Lecture Room, Monument and Washington Streets, at 4.30 p. m., by Thomas Lewis, M. D., University College, London, England.

Dr. Thomas Lewis, in charge of the heart station at University College, and Editor of *Heart*, has done important work in the study of cardiac conditions, and will present three lectures on the scientific study of the heart and its bearing on clinical medicine. He is the first clinical investigator who has filled the position of Herter Lecturer. The titles of his lectures will be announced later.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the LORD BALTIMORE PRESS, Baltimore. Subscriptions, $2.00 a year (foreign postage, 50 cents), may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for twenty-five cents each. Single copies may also be procured from the BALTIMORE NEWS CO., Baltimore.